A.M.A.

American Journal of DISEASES OF CHILDREN

FEBRUARY 1955
VOLUME 89 NUMBER 2

PROSTHESES FOR THE JUVENILE AMPUTEE
GEORGE T. AITKEN, M.D., ET AL.

DISCORDANT MONOZYGOTIC TWINS
JOSEF WARKANY, M.D., ET AL.

SALICYLATE POISONING
F. H. HARVIE, M.D., ET AL.

AMINO-ACIDURIA, HYPOPHOSPHATEMIA, AND RICKETS IN LEAD POISONING
J. JULIAN CHISOLM Jr., ET AL.

THERAPY OF THE NEPHROTIC SYNDROME
LAWRENCE GREENMAN, M.D., ET AL.

JAUNDICE IN MUCOVISCIDOSIS (FIBROCYSTIC DISEASE OF PANCREAS)
CHRISTOS D. GATZIMOS, M.D., ET AL.

ALLERGENICITY OF MODIFIED AND PROCESSED FOODSTUFFS
BRET RATNER, M.D., ET AL.

OBSERVATIONS ON TRICHINOSIS
LELABELLE C. FREEMAN, M.D., ET AL.

NITROFURANTOIN THERAPY OF URINARY TRACT INFECTIONS IN CHILDREN
S. HARRIS JOHNSON III, M.D., ET AL.

TEN-DAY TREATMENT OF PINWORM INFECTION WITH PIPERAZINE
LIEUT. VIRGIL M. HOWIE

COMPLETE CONTENTS ON FIRST PAGE

AMERICAN MEDICAL ASSOCIATION Publication

Provides a protein margin of safety

- **for greater nitrogen retention**
- **for firmer muscle mass**

LIQUID

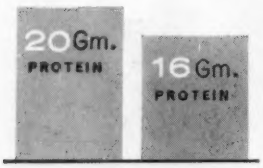
POWDERED

LACTUM

NUTRITIONALLY SOUND FORMULA FOR INFANTS

In the bottle-fed infant, a higher protein intake, with greater nitrogen retention, results in firmer muscle mass, better tissue turgor and better motor development.[1] A protein intake that does not maintain positive nitrogen balance "cannot be considered optimal or even safe for any length of time."[2]

During the first year of life, the infant's nourishment is derived primarily from his formula. Hence it is especially important that the formula be generous in protein. The usual Lactum® feedings provide 2 Gm. protein per pound of body weight—25% more than the Recommended Daily Allowance of 1.6 Gm. per pound (3.5 Gm. per kilogram).



Lactum formula for a 10 lb. infant

Recommended Daily Allowance for a 10 lb. infant

1. Jeans, P. C., in A.M.A. Handbook of Nutrition, Philadelphia, Blakiston, 1951, pp. 275-296. 2. Stare, F. J., and Davidson, C. S., in The Proteins, American Medical Association, 1945.

MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA, U.S.A. MEAD

TABLE OF CONTENTS

VOLUME 89 FEBRUARY 1955 NUMBER 2

ORIGINAL ARTICLES

PAGE

Prostheses for the Juvenile Amputee
George T. Aitkin, M.D., and Charles H. Frantz, M.D., Grand Rapids, Mich. ... 137

Discordant Monozygotic Twins
Josef Warkany, M.D., and Theodore K. Selkirk, M.D., Cincinnati ... 144

Salicylate Poisoning
F. H. Harvie, M.D., Philadelphia, and R. B. Singer, M.D., Boston ... 149

Amino-Aciduria, Hypophosphatemia, and Rickets in Lead Poisoning
J. Julian Chisolm Jr., M.D.; Helen C. Harrison, Ph.D., Baltimore; Walter R. Eberlein, M.D., Boston, and Harold E. Harrison, M.D., Baltimore, with the Technical Assistance of Flo C. Mohr, A.B. ... 159

Therapy of the Nephrotic Syndrome
Lawrence Greenman, M.D.; F. A. Weigand, M.D., and T. S. Danowski, M.D., Pittsburgh ... 169

Jaundice in Mucoviscidosis (Fibrocystic Disease of Pancreas)
Christos D. Gatzimos, M.D., and Richard H. Jowitt, M.D., Indianapolis ... 182

Allergenicity of Modified and Processed Foodstuffs
Bret Ratner, M.D.; Samuel Untracht, M.D., New York; Lloyd V. Crawford, M.D., Memphis; H. John Malone, M.D., Manchester, Conn., and Mary Retsina, M.D., New York ... 187

Observations on Trichinosis
Lelabelle C. Freeman, M.D.; Frederick J. Brady, M.D.; Althea D. Kessler, M.D., and Roland B. Scott, M.D., Washington, D. C. ... 194

Nitrofurantoin Therapy of Urinary Tract Infections in Children
S. Harris Johnson III, M.D., and Matthew Marshall Jr., M.D., Pittsburgh ... 199

Ten-Day Treatment of Pinworm Infection with Piperazine
Lieut. Virgil M. Howie (MC), U. S. A. F. ... 202

Neonatal Blood Pressure Studies
Abraham I. Schaffer, M.D., New York ... 204

Inhalant Allergens in Management of Atopic Dermatitis
Louis Tuft, M.D., Philadelphia ... 210

Hematuria as Manifestation of Sickle-Cell Anemia in Children
Robert L. Vernier, M.D., Little Rock, Ark. ... 221

CASE REPORTS

Acquired Hemolytic Anemia
J. M. Bowman, M.D., New York ... 226

Arthrogryposis Multiplex Congenita in Identical Twins
Earle L. Lipton, M.D., Syracuse, N. Y., and Sydney H. Morgenstern, M.D., Chicago ... 233

Prolonged Septic Leptospirosis
Harry J. Lawler, M.D., Billings, Mont. ... 237

Hemorrhagic Infarction of Testis in Newborn
Capt. Jimmie L. Rhyne (MC), U. S. Army Reserve; Lieut. Col. Frank A. Mantz Jr. (MC), U. S. Army, and Col. John F. Patton (MC), U. S. Army ... 240

PROGRESS IN PEDIATRICS

Presentation of the John Howland Medal and Award of the American Pediatric Society to Dr. Bela Schick
Horace L. Hodes, M.D., New York ... 246

REGULAR DEPARTMENTS

Abstracts from Current Literature ... 255

News and Comment ... 181, 239, and 254

Books ... 275

A. M. A.
American Journal of Diseases of Children

VOLUME 89 FEBRUARY 1955 NUMBER 2

COPYRIGHT, 1955, BY THE AMERICAN MEDICAL ASSOCIATION

EDITORIAL BOARD

ROBERT BARRETT LAWSON, Chief Editor
1000 N. W. 17th St., Miami 36, Fla.

A. A. WEECH, Cincinnati
FRANCIS SCOTT SMYTH, San Francisco
ROGER L. J. KENNEDY, Rochester, Minn.
JAMES L. WILSON, Ann Arbor, Mich.
WOLF W. ZUELZER, Detroit

AUSTIN SMITH, Editor, A. M. A. Scientific Publications
GILBERT S. COOPER, Managing Editor, Specialty Journals

AMERICAN MEDICAL ASSOCIATION
Scientific Publications

The Journal of the American Medical Association. Weekly. Annual Subscription Price, $15.00.

Quarterly Cumulative Index Medicus. Issued Twice a Year. Subscription Price, Calendar year, $20.00.

A. M. A. Specialty Journals
Monthly

A. M. A. Archives of Internal Medicine. Paul S. Rhoads, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price, $10.00; Canada, $10.50; Foreign, $11.50; individual copy, $1.00.

A. M. A. Archives of Dermatology. Paul A. O'Leary, M.D., Chief Editor, 200 First St. S.W., Rochester, Minn. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Ophthalmology. Francis Heed Adler, M.D., Chief Editor, 313 S. 17th St., Philadelphia 5. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Surgery. Waltman Walters, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price, $14.00; Canada, $14.50; Foreign, $15.50; individual copy, $1.25.

A. M. A. American Journal of Diseases of Children. Robert Barrett Lawson, M.D., Chief Editor, 1000 N.W., 17th St., Miami 36, Fla. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Pathology. Paul R. Cannon, M.D., Chief Editor, Department of Pathology, University of Chicago, The School of Medicine, 950 E. 59th St., Chicago 37. Price, $8.00; Canada, $8.50; Foreign, $9.25; individual copy, $1.00.

A. M. A. Archives of Neurology and Psychiatry. Tracy J. Putnam, M.D., Chief Editor, 450 N. Bedford Drive, Beverly Hills, Calif. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Otolaryngology. George M. Coates, M.D., Chief Editor, 1721 Pine St., Philadelphia 3. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Industrial Health. Prof. Philip Drinker, Chief Editor, Dept. of Industrial Hygiene, Harvard University School of Public Health, 55 Shattuck St., Boston 15. Price, $8.00; Canada, $8.50; Foreign, $9.00; individual copy, $1.00.

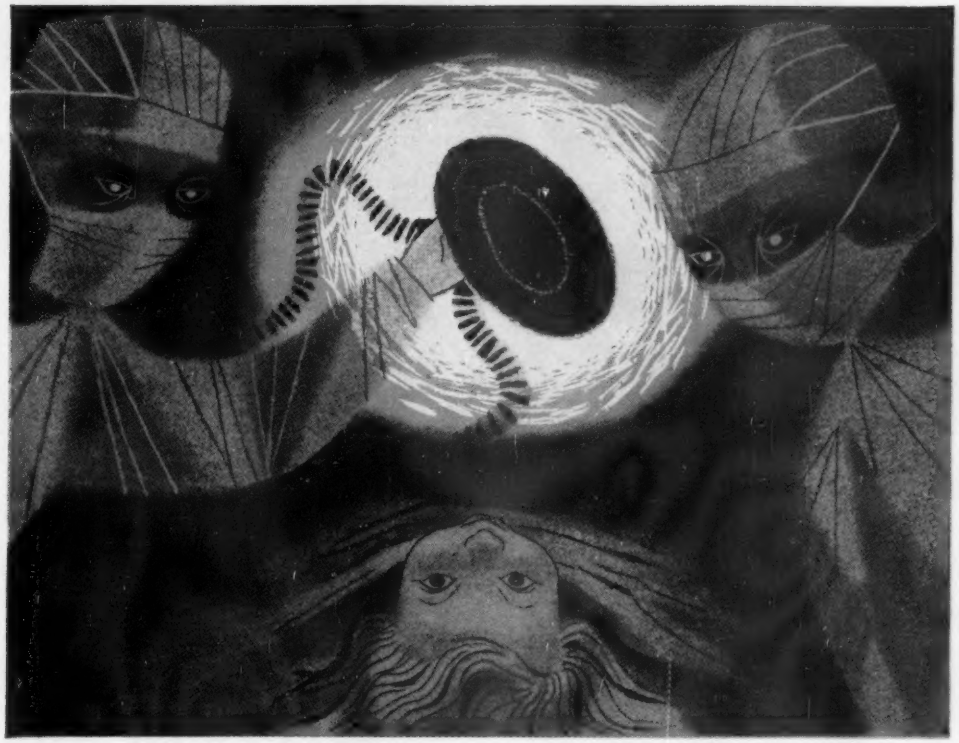
Checks, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

Published Monthly by

AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 4, 1911, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00



NO
NIGHTMARE
OF FEAR
...no pain
...no memory

THE terrifying fight to breathe as the mask is lowered over the face . . . this is an experience your pediatric patients need never know. For now, with the rectal administration of PENTOTHAL Sodium, they never know the operating room. They go to sleep in the comfort and security of their own hospital beds before surgery . . . and wake up there afterward.

Rectal PENTOTHAL may be used to attain levels ranging from preanesthetic sedation or hypnosis to basal hypnoses. It may serve as an adjunct to general anesthesia and as the sole agent in a variety of minor procedures. Dosage of inhalation agents is reduced, emergence delirium and postanesthetic nausea are minimized.

Abbott

Pentothal® Sodium

(Thiopental Sodium, Abbott)

By Rectum

Send for literature—
"PENTOTHAL Sodium by Rectum" . . . results from nearly 4,000 cases.

502068

Instructions to Contributors

Communications regarding editorial management, subscriptions, reprints, etc., should be addressed to Specialty Journals, American Medical Association, 535 North Dearborn Street, Chicago 10.

Articles, book reviews, and other materials for publication should be addressed to the Chief Editor of the Specialty Journal concerned. Articles are accepted for publication on condition that they are contributed solely to that journal.

An original typescript and the first carbon of an article should be provided; it must be double or triple spaced on one side of a standard size page, with at least a 1-inch margin at each edge. An article in English by a foreign author should be accompanied by a draft in the author's mother tongue. Improvised abbreviations should be avoided.

The main title of an article may not contain more than ninety characters and spaces; a subtitle may be of any length. The subtitle should be sufficiently detached from the main title that a punctuation mark as strong as a colon can be used in the Table of Contents to separate it from the main title; it must not begin with "with."

The author's name should be accompanied by the highest academic or medical degree which he holds. If academic connections are given for one author of an article, such connections must be given for all other authors of the article who have such connections.

Typographic considerations necessitate that the first paragraph of an article contain not fewer than thirty words. A Case Report must be preceded by an introductory paragraph containing at least thirty words before the details of the case are given.

Material quoted from another publication must be quoted exactly if the original is in English—spelling, capitalization, punctuation, etc., unchanged. Material taken largely from another publication must be credited to the original author, whether quoted exactly or merely abstracted. If such material is quoted indirectly, the author must be careful to leave no complete sentence of the original unaltered. Use of uncredited quotations will be sufficient cause for rejection of an article.

Each article should be accompanied by a summary in the present tense, presenting the main points of the article, but in somewhat more generalized terms than in the article itself.

If it is necessary to publish a recognizable photograph of a person, the photograph must be accompanied by written permission of the subject himself if an adult, or of the parents or guardian if a child, to publish his photograph. An illustration which has been published in another publication must be accompanied by written permission from the author and the original publisher to reproduce it in an A. M. A. Specialty Journal.

The maximum illustration allowance is ten illustrations within a total of 100 sq. inches or $100, whichever is of greater advantage to the author. When no restrictions are placed by the author upon cropping, reducing, and grouping, the publisher is often able to use twenty or more illustrations in one article with the $100 allowance. Submit sharp prints of the following sizes, 2½″ wide × 2½″ or 3½″ high, 3½″ wide × 2½″ high, and 5½″ or 7″ wide × 3½″ high, to minimize reduction and/or cropping. Oversized originals should be photographed and a print submitted. Large photomicrograph prints will be reduced in scale unless portions to be cropped are indicated by the author.

Any cut-off marks should be made on the margins or mountings rather than on the illustration itself. Charts and drawings should be in black ink on hard, white paper. Lettering must be large enough to permit necessary reduction. Glossy prints of x-rays are requested. Paper clips should not be used on prints, since their mark shows in reproduction, as does writing on the back of prints with hard lead pencil or stiff pen. Labels should be prepared and pasted to the back of each illustration showing its number, the author's name, an abbreviated title of the article, and top plainly indicated. Charts and illustrations must have descriptive legends, grouped on a separate sheet. Tables must have captions. IT IS PREFERRED THAT ILLUSTRATIONS BE UNMOUNTED.

References to the literature should be numbered in the order in which they are referred to in the text or listed in alphabetical order without numbers. A chronological arrangement, with all entries for a given year alphabetized according to the surname of the first author, may be used if preferred. References should be typed on a special page at end of manuscript. They should conform to the style of the Quarterly Cumulative Index Medicus, and must include, in the order given, name of author, title of article (with subtitle), name of periodical, with volume, page, month—day of month if weekly or biweekly—and year. Names of periodicals should be given in full or abbreviated exactly as in the Quarterly Cumulative Index Medicus. Reference to books must contain, in the order given, name of author, title of book, city of publication, name of publisher, and year of publication. Titles of foreign articles, if originally in a generally known Romance or Germanic tongue, must either all be in English translation or all be in the original language. Titles in other languages must be translated. The author must assume responsibility for the accuracy of foreign titles.

Matter appearing in the A. M. A. Specialty Journals is covered by copyright, but as a rule no objection will be made to its reproduction in a reputable medical journal if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the A. M. A. Specialty Journals, or in any other publications issued by the Association, will not be permitted.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **Chicago 10**

Thank you doctor
for telling mother about...

- The Best Tasting Aspirin you can prescribe
- The Flavor Remains Stable down to the last tablet
- Bottle of 24 tablets 15¢ (2½ grs. each)

We will be pleased to send samples on request

THE BAYER COMPANY DIVISION of Sterling Drug Inc., 1450 Broadway, New York 18, N. Y.

HOW TO SIMPLIFY THE MANAGEMENT OF

Anticipate milk allergy prenatally—then feed MULL-SOY instead of cow's milk from birth whenever either parent or a sibling has a history of major allergy.[1]

Suspect milk allergy postnatally—diagnose with a 48-hour MULL-SOY test feeding whenever one or more of these symptoms persists: eczema, pylorospasm, colic, diarrhea, constipation, rhinitis, asthma, anorexia, or persistent hyperirritability.[2]

Replace cow's milk with MULL-SOY *whenever* milk allergy is a complication.

references: 1. Glaser, J., and Johnstone, D. E.: J.A.M.A. 153:620, 1953.
2. Clein, N. W.: Pediat. Clin. North America, Philadelphia, Saunders, Nov., 1954, p. 949.

INFANT MILK ALLERGY

Soy alternative to evaporated milk

MULL-SOY Liquid

In 15½-fl.oz. tins. Start with a 1:3 dilution with water, strengthen gradually to 1:1. Add carbohydrate of choice as required.

MULL-SOY®

Liquid or Powdered

pioneer hypoallergenic *alternative* to cow's milk
fits *any* formula in which cow's milk has been used

Soy alternative to dried whole milk

MULL-SOY Powdered

In 1-lb. tins. Start with 1 level tablespoonful to 4 fl.oz. water, strengthen gradually to 1 tbsp. to 2 fl.oz. water. Add carbohydrate of choice as required.

Write for folder "Simplified Feeding Schedules for Milk-Allergic Babies," and attractive recipe booklets.

Borden's PRESCRIPTION PRODUCTS DIVISION
® 350 Madison Avenue, New York 17

Enriched Bread in Special Diets

THE many advantages of enriched bread in special diets are all too seldom recognized or appreciated. Hence, the physical, physiologic, nutritional, and dietetic values of enriched bread warrant detailed enumeration.

The open, soft texture of enriched bread enables its easy mastication, its ready absorption of digestive juices, and its prompt and thorough digestion. Reflexly, its appetizing eating qualities enhance the digestive processes. Since bread is free from coarse or harsh vegetable fiber, it proves nonirritating mechanically to the gastric and intestinal mucosa. In metabolism its minerals are neutral.

Enriched bread contains less than 0.2 per cent fibrous material, yielding insignificant amounts of indigestible residue. It contains only 3 per cent of fat, negligible amounts of purines, no cholesterol, and does not interfere with the digestive or absorptive processes. It contributes to a desirable texture of the food mass throughout the intestine. The contained nutrients are absorbed gradually.

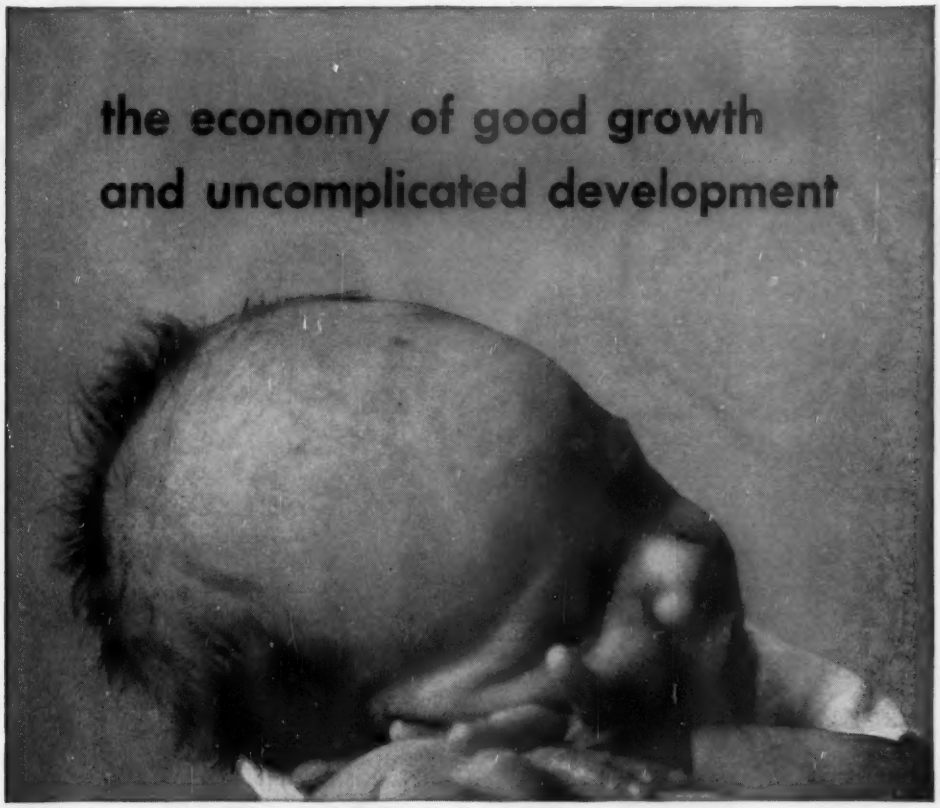
Nutritionally, enriched bread supplies valuable amounts of biologically valuable protein, 8.5 per cent; easily digestible carbohydrate, essentially starch and dextrins, 52 per cent; and minerals, 1.8 per cent. Enriched bread provides notable amounts of vitamins and minerals: each 100 grams supplies on the average 0.24 mg. of thiamine, 0.15 mg. of riboflavin, 2.2 mg. of niacin, 88 mg. of calcium, 92 mg. of phosphorus, and 2.6 mg. of iron. Also it provides 275 calories of nutrient energy per 100 grams.

Enriched bread, in either fresh or toasted form, contributes to the eating pleasure of many other nutritious foods. Its neutral flavor permits it to blend well with other foods.

For these reasons, enriched bread enjoys a prominent place in a great variety of special diets—soft, low residue, low purine or cholesterol diets, general hospital diets, as well as diets low or high in carbohydrates, in proteins, or in calories.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

AMERICAN BAKERS ASSOCIATION
20 NORTH WACKER DRIVE • CHICAGO 6, ILLINOIS



SIMILAC POWDER—*physiologic food during the first year of life*—

To assure sound growth and reduce many of the complications commonly encountered in the first year of life, the full, balanced Similac formula provides: fat, protein and carbohydrate closely approximating the content of human breast milk in quality and quantity; a full complement of known essential vitamins in adequate amounts; an adjusted mineral content; a soft, fluid curd with zero tension, assuring rapid and easy digestion.

SIMILAC POWDER—*stable in price . . . an economy in feeding*—

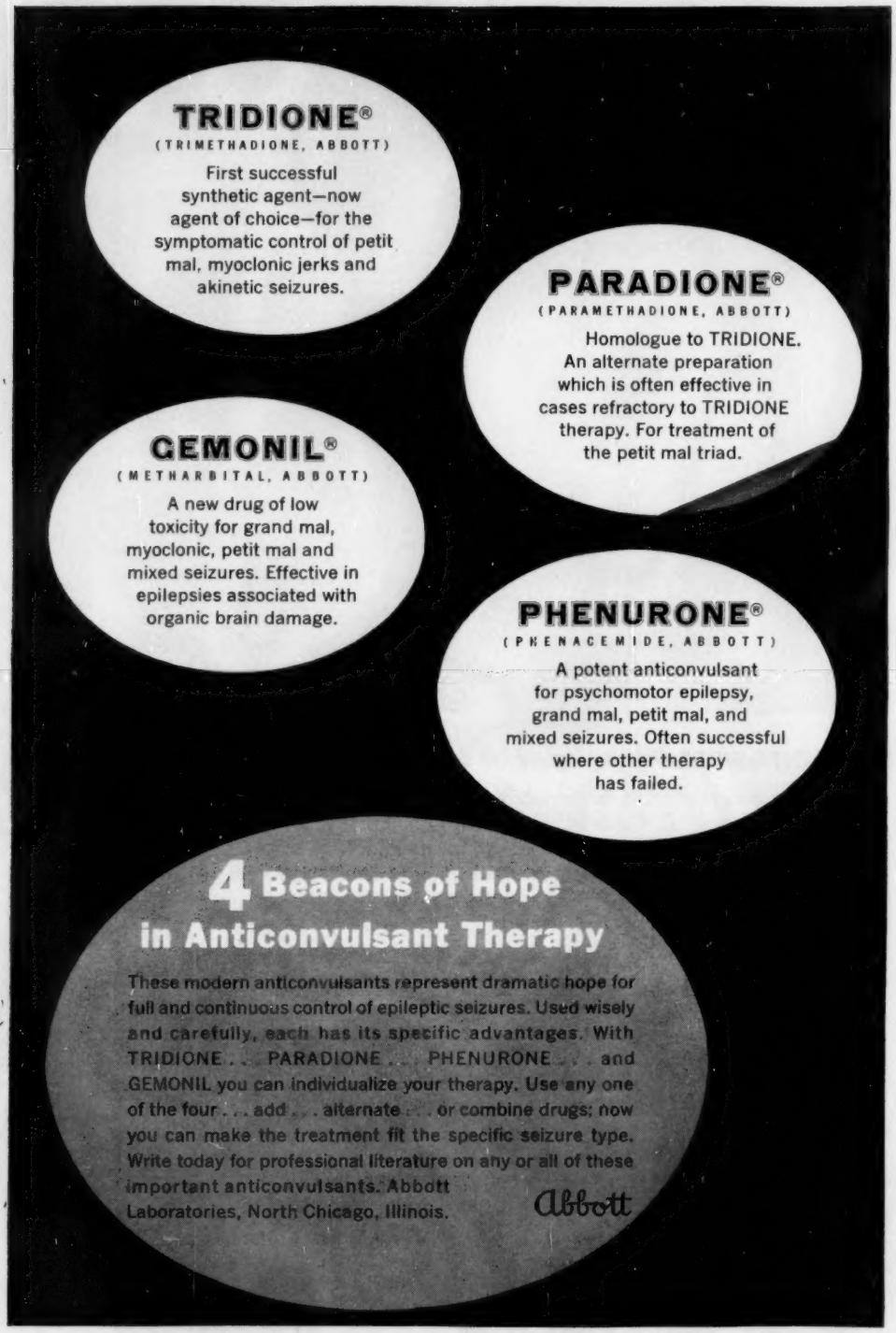
With food costs at or near an all-time high, the price of Similac has remained relatively constant since 1923. Similac with its complete modification and added vitamins is virtually the same in price as vitamin-supplemented whole-milk feeding – and in many instances actually affords greater economy.

SIMILAC *powder*

There is no closer equivalent to the milk of healthy, well-nourished mothers

SUPPLIED:
Tins of 1 lb., with measuring cup. Similac is also available as concentrated Liquid in tins of 13 fl. oz.

M & R LABORATORIES, *Columbus 16, Ohio*

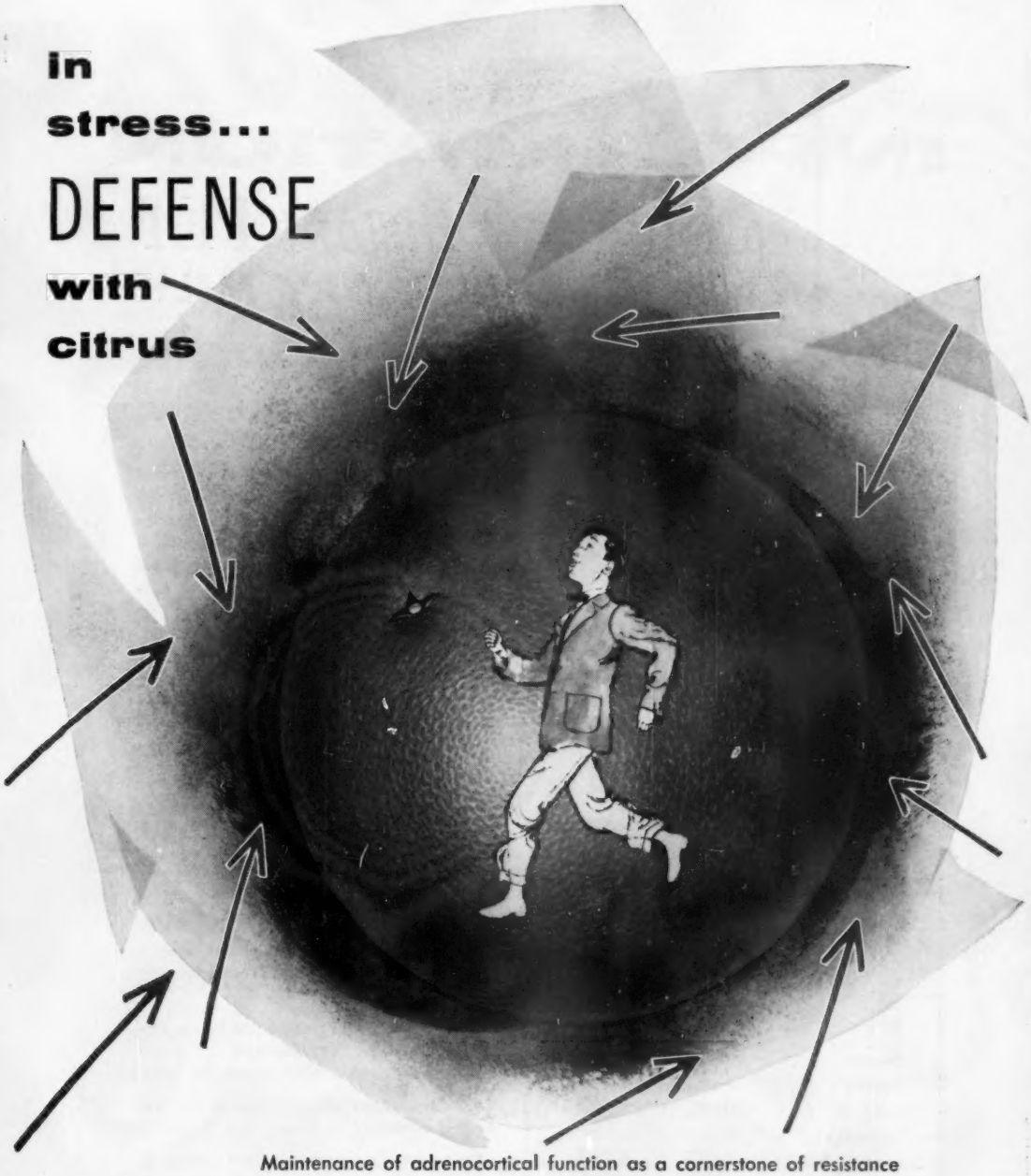

TRIDIONE®
(TRIMETHADIONE, ABBOTT)
First successful synthetic agent—now agent of choice—for the symptomatic control of petit mal, myoclonic jerks and akinetic seizures.
PARADIONE®
(PARAMETHADIONE, ABBOTT)
Homologue to TRIDIONE. An alternate preparation which is often effective in cases refractory to TRIDIONE therapy. For treatment of the petit mal triad.
GEMONIL®
(METHARBITAL, ABBOTT)
A new drug of low toxicity for grand mal, myoclonic, petit mal and mixed seizures. Effective in epilepsies associated with organic brain damage.
PHENURONE®
(PHENACEMIDE, ABBOTT)
A potent anticonvulsant for psychomotor epilepsy, grand mal, petit mal, and mixed seizures. Often successful where other therapy has failed.
4 Beacons of Hope in Anticonvulsant Therapy
These modern anticonvulsants represent dramatic hope for full and continuous control of epileptic seizures. Used wisely and carefully, each has its specific advantages. With TRIDIONE . . . PARADIONE . . . PHENURONE . . . and GEMONIL you can individualize your therapy. Use any one of the four . . . add . . . alternate . . . or combine drugs; now you can make the treatment fit the specific seizure type. Write today for professional literature on any or all of these important anticonvulsants. Abbott Laboratories, North Chicago, Illinois.
Abbott

502051A

in stress...

DEFENSE

with citrus



Maintenance of adrenocortical function as a cornerstone of resistance in stressful life situations helps prevent disorders characteristic of the general adaptation syndrome. Since vitamin C is essential to production of anti-stress hormones by the adrenal cortex, an ample intake of readily utilized *natural vitamin* C as provided by citrus fruits and juices is desirable.

FLORIDA CITRUS COMMISSION • ***Lakeland, Florida***

FLORIDA *Citrus*

ORANGES • GRAPEFRUIT • TANGERINES

INFORMATION

about New *Instant* PET NONFAT DRY MILK

. . . why it helps with the dietary management of the very young infant and the older child.

- **For the infant with diarrhea** or other disease states where digestion is impaired, *Instant* PET Nonfat Dry Milk maintains needed high protein, mineral, and vitamin levels while eliminating fat from the diet and supplying only half the calories of whole milk.
- **For the premature infant** or infants with limited capacity, where increased levels of protein and calcium and lower fat are desirable, *Instant* PET Nonfat Dry Milk provides an ideal means of fortifying the milk mixture.
- **For the overweight child** on a calorie-restricted diet, *Instant* PET Nonfat Dry Milk – with 50% less calories than whole milk – furnishes all of milk's proteins, vitamins, and minerals which contribute to normal growth.
- *Instant* PET Nonfat Dry Milk is one of the most useful foods whenever a diet low in fat, moderately low in calories, but high in protein and calcium is indicated.

Reconstituted* as compared with whole milk

	Pet Nonfat Milk*	Whole Milk (Average)
Protein	3.5%	3.3%
Lactose	4.8%	4.7%
Minerals . . . (Includes)	0.8%	0.7%
Calcium . . .	0.13%	0.13%
Phosphorus .	0.10%	0.10%
Sodium . . .	0.05%	0.05%
Potassium . .	0.15%	0.15%
Fat	0.10%	3.80%
Moisture . . .	90.81%	87.50%
Calories (qt.) .	332	646

*1 cup (3¼ oz.) Instant PET Nonfat Dry Milk plus water to make 1 qt.

SOME SPECIAL ADVANTAGES OF *INSTANT* PET NONFAT DRY MILK

Fresh milk flavor – it's delicious . . . can be used as a beverage or in cooking.

Easy-to-prepare – it's instantly soluble in cold water, a significant improvement over customary nonfat dry milk.

Easy-to-store – it's packed in a handy airtight glass jar . . . no leakage . . . no refrigeration needed while in powder form.

Readily obtainable – it's available in food stores everywhere.

Low cost – it's a concentrated source of nonfat milk at less than half the price of ordinary milk.

Developed by Pet Milk Company, makers of the original evaporated milk

PET MILK COMPANY, ARCADE BUILDING, ST. LOUIS 1, MO.

PROSTHESES FOR THE JUVENILE AMPUTEE

GEORGE T. AITKIN, M.D.
and
CHARLES H. FRANTZ, M.D., Grand Rapids, Mich.

THE JUVENILE amputee has been afforded much interest in the past few years. Society has realized that children as a population percentage group have become victims of mechanization as well as the adult. Functional rehabilitation is now a byword in industry. Communities and organizations sponsor and maintain rehabilitation work shops and training centers for the handicapped.

The child amputee, as a segment of the population and an important potential in the coming generation, must be rehabilitated.

The contributions of orthopedic surgeons, technical skills of the physical and occupational therapists, and the rapid advances in the prosthetic field have allowed many congenitally handicapped children to anticipate competition with their normal brethern in the fields of economic endeavor. Many juvenile amputees have a greater economic potential than the child with cerebral palsy or the severely paralyzed postpoliomyelitis victim.

The child is a plastic growing human with a progressively developing skeleton and a wide range of adaptability. His motor patterns are not fixed. An analysis of a large number of juvenile amputees have demonstrated several pertinent facts.

1. Short stumps, excessive scars, neuromata and spur formation, likely to plague the adult, are seldom cause for dysfunction in the child.

2. Careful examination of the child and his stump will seldom indicate the necessity for surgical conversion or refashioning of the stump.

3. The juvenile's problem is usually the need for a comfortable mechanically sound prosthesis and proper training in its use.

From the Mary Free Bed Guild Children's Hospital and Orthopedic Center.

There has been query and debate relative to the most opportune time for the fitting of a prosthesis to the child. Not infrequently a serious error is committed in assuming that the rapidly growing child can get by with crutches or an empty sleeve until he reaches a relatively late stage of his maturity. The fact that growth and development are dependent upon exercise and functional activity is overlooked.

It is quite evident that, to function in a prosthesis, the recipient must have the potential skill for manipulating the device. This potential implies motor and emotional development to a stage where the child will tolerate and mobilize an appliance. With maturity at a satisfactory level, it follows that the prosthesis must be comfortable and mechanically sound to obtain function.

Eight months of age finds the child showing a special interest in pulling himself to his feet. He holds the sides of the crib or playpen and may stand alone. Fifteen months demonstrates him to be no longer a creeping baby. He toddles about with a sense of locomotion.

The child is on the loose by 18 months. Seldom does he walk; he runs. He is getting his legs under control. The progress of this kinesthetic sense is an orderly developing basic motor pattern. There are, of course, variations in the chronological development of the motor skill. Some children may be slightly earlier. It is, however, not unusual to observe a child with late independent standing balance or walking. This may be as late as 20 or 22 months. Experience has proved that youngsters as young as 12 months of age can stand on an artificial limb and quickly learn to walk (Figs. 1, 2, and 3).

Fig. 1.—D. D. Placed in lower-extremity prostheses at one year of age.

This young upright human needs two legs for progression and will adapt himself in a natural way to the appliance. The prosthesis always becomes more a part of the child than it ever does of the adult because the youngster grows up with it. He quickly learns to put his weight to the limb and will swing it for ambulation.

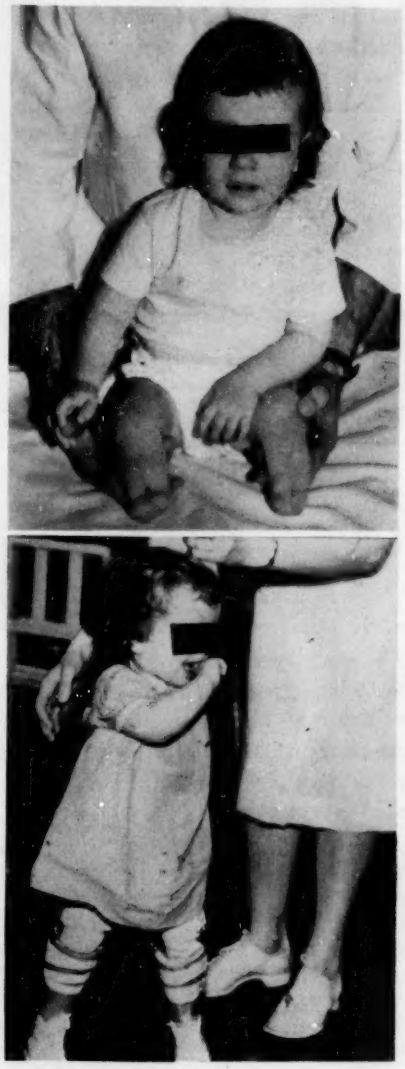
Functioning the amputation stump in a prosthesis will aid in stimulating growth of the skeleton and soft parts. The best walkers on artificial limbs are those who were fitted at an early age.

The upper extremity prosthesis must await the development of a sufficient maturity level to tolerate and mobilize it. This pattern again is an orderly progression of motor behavior.

The child develops index-finger-thumb prehension at 40 weeks of age. His grasp is good but release is crude. Two years finds him turning door knobs (pronation and supination). He does, however, overgrasp and overrelease. When 3 years old, the child is able to put on his shoes and unbutton some of his front buttons. He is able to manipulate clay into various forms (flat cakes and balls). Attempts at finer motor coordination will demonstrate a fine tremor.

Four years finds him dressing and undressing himself. He manages buttons and manages pencil and crayon fairly well. He is able to copy a square. He uses scissors and does a good job of following a straight line in his cutting. He will attempt to finger piano keys. Psychologically, the child is responsive and is proud of his accomplishments. He will usually listen to reason and take verbal instruction. At this age he is not too erratic and is becoming more stable emotionally and intellectually.

Fig. 2—J. W. Below-knee amputee. Placed in prostheses at 18 months of age. Walked independently in three and one-half months.



The 4-year-old level of intellectual and motor development has been proved to be a very satisfactory period for applying an upper extremity prosthesis. The appliance, whether a below-elbow or above-elbow type, can be well fitted and harnessed. At this age the child will readily functionalize a voluntarily opening terminal device (Figs. 4 and 5).

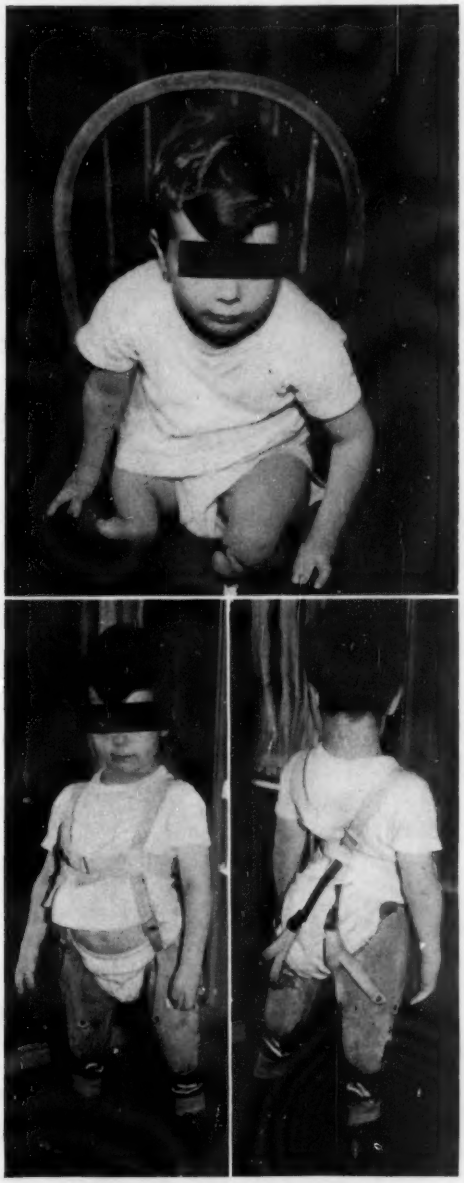


Fig. 3.—J. M. Congenital abnormalities of the lower extremities. No femoral heads; dislocated hips. Placed in prostheses at 2½ years of age. Walked independently in four months.

An artificial arm applied at this age will allow a full year of training and acquaintance with the device, and an acceptable degree of skill will be mastered to afford good performance when he enters kindergarten.

This youngster at 4 years of age is a component of the family group. He is encouraged, coached, coaxed, disciplined, and conditioned as he matures. Throughout his formative years he gradually learns what is right and what is wrong. He is dependent; he listens and learns. Countless episodes will exert an everlasting influence on his outlook.

The dependency of the child on his family at this period of life demands complete and enthusiastic cooperation of the parents. They must see the appliance work and appreciate its advantages; know what it will do and what it will not do. They must be willing to spend time in the home to augment the initial training period. Insistence, integrated with good judgment for wearing the prosthesis during house tasks and play, plus encouragement, will go far in developing skill and confidence in the youngster.

In early school days some of the affection for the mother is transferred to the teacher. She, in sorts, is an auxiliary mother. The teacher aids the mother in developing the child's social behavior and awareness of himself in relation to others. In such a capacity, the teacher wields a powerful influence on her pupil. Young amputees should attend public school. Elementary teachers and principals should recognize the handicap and participate in the everyday training of skills. In some instances amputees are prohibited from attending public schools. Early acceptance within a normal environment is important to the child psychologically. Most young amputees are able to perform on the same level as their playmates do. It is sometimes amazing how fast the child will learn to do things after proper fitting and instruction.

In the schoolroom, understanding on the part of the teacher will further the development of everyday skills. His playmates at

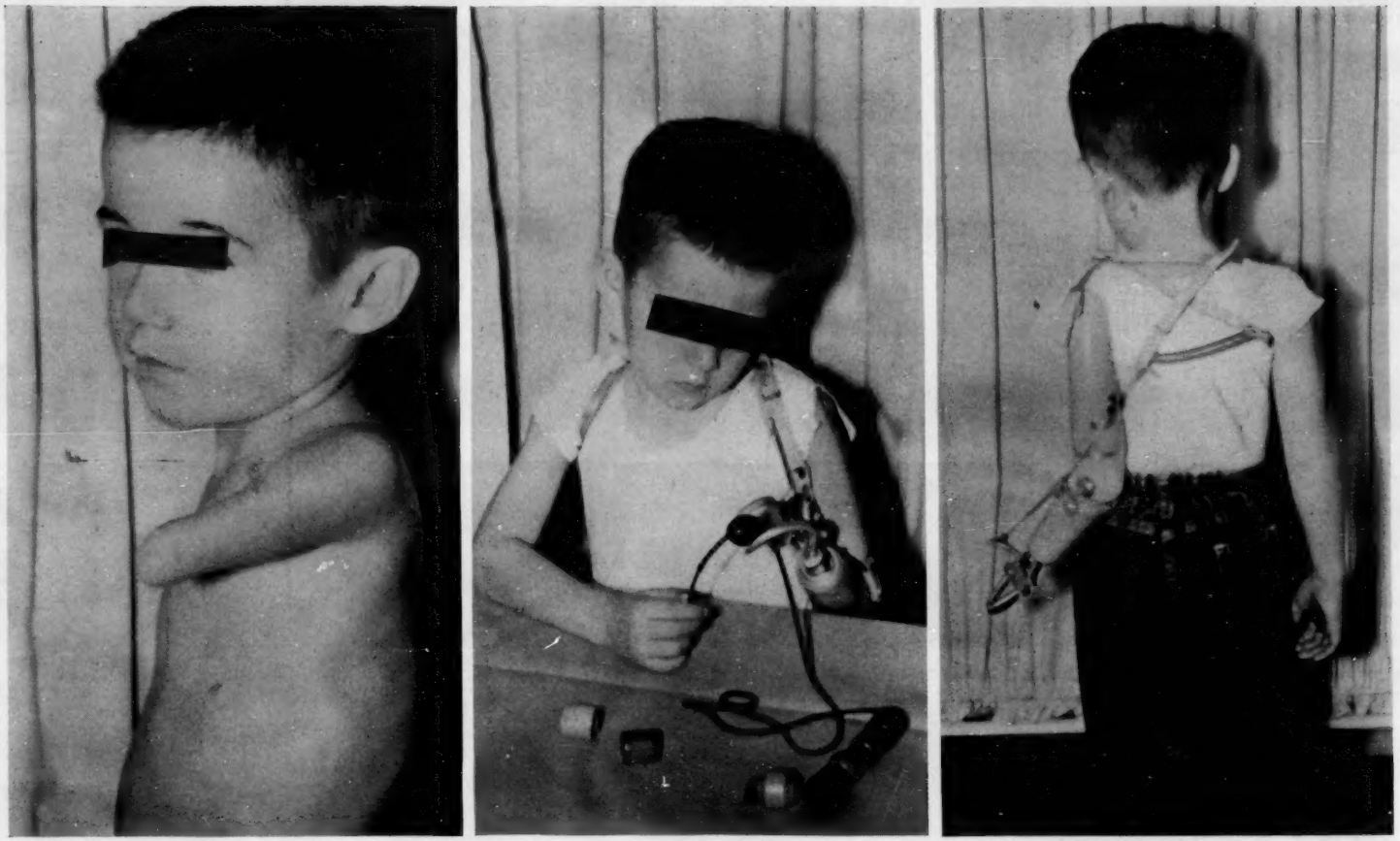
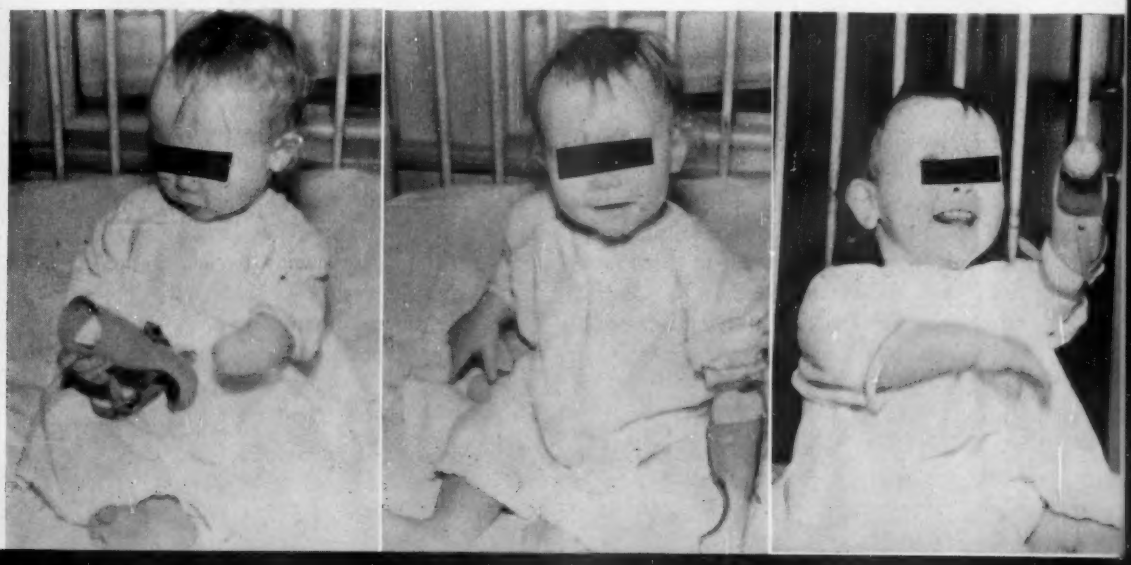


Fig. 4.—T. S. Four-year-old boy is congenital above-elbow amputation. Placed in conventional above-elbow prostheses with voluntary-opening terminal device at 4 years of age.

Fig. 5.—S. D. Six years old. Congenital below-elbow amputee.

Fig. 6.—B. M. Thirteen months of age. Congenital below-elbow amputee. Fitted with forearm device indented to hold a feeding bottle. This child tolerated the apparatus. In six weeks' time she held her own bottle.



this age are inquisitive and curious. Teacher, parent, or therapist should show the playmates the prosthesis and let it be known why it is being worn. They should allow the children to ask a few questions. With curiosity satisfied, they will pay little further attention to the appliance. This procedure should be followed with the young amputee's introduction to school. It will facilitate his adjustment to the group.

There is at present nothing in the literature indicating that a young child will accept and functionalize an upper extremity prosthesis. Youngsters in their second year of life tolerate a lightweight apparatus without a mechanically operated terminal device (Fig. 6).

At the tender age of 1 to 2 years, the hand function is unskilled. Pronation and supination are present, but the grasp and release mechanism is poorly developed synergically. A passive rubber mitten curved and sized to the opposite normal member allows for gross grasping and holding at the normal distance from the body. The child will tolerate the apparatus, hold a bottle, and do things commensurate with his or her age.

It is a peculiar phenomenon of psychology that the recommendation for a lower extremity prosthesis is readily acceptable, but contrarily, there is at times a tendency to reject an upper-extremity prosthesis. This phenomenon usually pertains to girls, with the reluctance exhibited by the mother.

In the congenital group, this refusal may be nurtured by deep roots of guilt activated by the fear of a hereditary taint. In the traumatic group the guilt often springs from a deep feeling of negligence in reference to the episode causing the accident. Both these basic reactions manifest themselves and may convey the impression of a blind reluctance to accept the presence of a functional disability. An excuse not unusual is the revulsion to the cosmetic appearance of the terminal hook, it being unacceptable in social functions. It is understandable that such feeling on the part of the parents can be readily transferred to the child.

If the doctor observes that a comfortable mechanically sound prosthesis is not worn a goodly part of the day and skill development is lagging, the answer is usually half-hearted or no family cooperation. The solution, under such circumstances, lies in a complete open discussion with the parents. The mother must be shown that she, in herself, may be a problem which inadvertently is denying the child potential advantages in skill. Demonstrations to doubting or hesitant parents of what can be accomplished and answers to questions may reverse the antipathy. A well-trained child, one or two years older than the patient in question, demonstrating his or her skill with the terminal device and simple answers to the querying parent may change the whole picture.

It is fallacious to expect the young amputee to wear an upper-extremity prosthesis all of his waking hours. The goal is functional skill and appreciation of the prosthesis in offering the skill. The advantages of the appliance will be manifested in chores, schoolroom activities, social functions, and certain recreational activities (card games, checkers, chess, ping-pong, knitting, drawing, weaving, etc.).

The danger of a wooden forearm and a metallic hook is evidenced in body-contact sports. The prosthesis need not be worn during all such activities. This precaution should be considered in youngsters from 7 to 12 years of age. The explosion of physical energy in this age range makes the prosthesis during the excitement of play time a potential lethal weapon.

Smaller children, from 4 to 6 years of age, may be content to play with blocks, pull ropes, push trucks, dig holes, and manipulate other utensils. The advantage of the appliance during these activities is self-evident.

The appreciation of the child's stage of motor skill and emotional development should aid in forming a common-sense outlook toward the use of an upper-extremity appliance. The young amputee, properly guided, will show a progressive development in skill

with his artificial limb which, in varying degrees, tends to parallel his normal prehensile maturation pattern.

BIBLIOGRAPHY

Beekman, F.: Amputation During Childhood, S. Clin. North America **18**:425-431, (April) 1938.

Chittenden, R. F.: The Use of Prosthesis for Limb Defects in Children, Am. J. Surg. **86**:128-138 (Aug.) 1953.

Comer, J. F.: The Juvenile Amputee, J. M. A. Alabama **21**:81-86 (Oct.) 1951.

Craft, A. W. J.: Prostheses for Children, Lancet **1**:639-642 (May 13) 1944.

Gesell, A.; Ilg, E. L.; Ames, L. B., and Bullis, G. E.: The Child from 5 to 10, New York, Harper & Brothers, 1946.

Ilg, F. L.; Learned, J., and Ames, L. B.: Infant and Child in the Culture of Today: The Guidance of Development in Home and Nursery School, New York, Harper & Brothers, 1943.

Thomas, A., and Haddan, C. C.: Amputation Prosthesis: Anatomic and Physiologic Considerations, with Principles of Alignment and Fitting Designed for the Surgeon and Limb Manufacturer, Philadelphia, J. B. Lippincott Company, 1945.

DISCORDANT MONOZYGOTIC TWINS

Hypothyroidism

JOSEF WARKANY, M.D.
and
THEODORE K. SELKIRK, M.D., Cincinnati

DIFFERENCES in growth and development of monozygotic twins may be due to various causes. Inequalities in fetal blood supply account for early differences, and various environmental causes are under consideration for differences arising in postnatal life. If monozygotic twins are discordant in many respects, it is often not possible to find a common factor responsible for the dissimilarity.

In the cases reported below, hypothyroidism of one of the twins accounted for great differences in many physical and mental traits. The differences were marked at times but decreased later under intensive thyroid medication.

The twins are the only children of young, intelligent, and cooperative parents. The father's family history is noncontributory. Twinning had occurred in the mother's family. The mother's father was an identical twin who had twin grand-uncles. A maternal aunt became obese, tired, and chronically constipated when 17 years of age and improved on thyroid medication. The twin's mother was overweight at adolescence, had puffy eyes, and was without energy. Her basal metabolic rate was —47, and she received thyroid treatment (1 to 4 grains [0.06 to 0.26 gm.] per day) for about 12 years. After an early miscarriage, she became pregnant again. She took 3 grains (0.19 gm.) of thyroid daily throughout the pregnancy which resulted in the birth of the twins.

Leah R. H. and Myra E. H. were born on May 21, 1949, after a pregnancy of eight months. Leah was born first in cephalic presentation, but disengagement was delayed and instruments were used to terminate delivery. Her birth weight was 4 lb. 11 oz. (2,130 gm.). Myra was born later after a breech presentation. Her birth weight was 4 lb. 15 oz. (2,240 gm.). The entire delivery lasted 54 hours. The placenta and the membranes disintegrated, and their appearance did not contribute to the diagnosis of zygotism.

At first, Leah appeared entirely normal, and weight gain was satisfactory like that of her twin sister; they were so similar that they were mistaken for one another. At the age of three months, Leah's appetite declined, she showed a tendency to be cold with somewhat cyanotic extremities, and her skin color became yellowish. Dr. Philip C. Elliott, of Nashville, Tenn., recognized that she suffered from thyroid dysfunction and began treatment with thyroid tablets. At the age of four months, her weight had increased to 12 lb. 10 oz. (5,730 gm.), but her weight gain was below that of her sister. The mother states that Leah received from 1/10 to ¼ grain (0.006 to 0.015 gm.) of thyroid daily but could not tolerate ½ grain (0.03 gm.). In photographs taken at the age of six

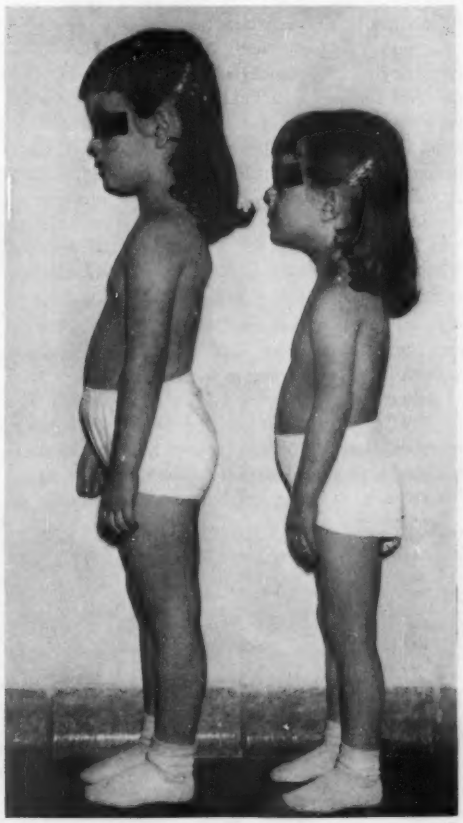
Fig. 1.—Hypothyroid twin at the age of 14 months.

From the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati College of Medicine.

months, the twins have very similar facial features, but Leah had to be propped up, while her sister could sit up without support. Both twins had mild attacks of pertussis when eight months old. At about that time Leah began to sit up, but she did not walk until 21 months of age. Her gait was insecure, she could not climb steps, and she did not talk. Towards the end of Leah's first year, thyroid was given irregularly; her color became more yellow and very pale, and her hemoglobin value was 7 gm. per 100 cc. She was treated with two blood transfusions, but from that time on her growth and development remained consistently behind that of Myra. When 14 months old she presented a definite picture of hypothyroidism (Fig. 1). She had edema of the eye lids, thick lips, a large tongue, yellowish color, particularly around the nose, a protruding abdomen, and chronic constipation. At that time a urinary infection set in which lasted intermittently to the age of 4 years. There were occasional attacks of fever, pyuria, and enuresis. During febrile periods, Leah had three mild convulsive seizures. When the child was about 3½ years old, the family changed residence, and Leah did not receive thyroid treatment for some time. She became lethargic, did not seem to grow at all for several months, and developed marked symptoms of hypothyroidism. At the age of 4 years, she was given increasing doses of thyroid, and distinct improvement was soon noticed. While receiving 1½ grains (0.09 gm.) of thyroid, she became more active, began to grow rapidly, and lost the symptoms of hypothyroidism. During her fifth year, thyroid medication was adapted according to her clinical course and varied between 1 and 2½ grains (0.07 and 0.16 gm.) per day. She began to talk at the age of 3 years.

In January, 1954, at the age of 4 8/12 years, she was admitted to the Children's Hospital because of a febrile episode. On admission her temperature was 102 F; it later rose to 104.6 F but returned to normal within four days. Her weight was 32½ lb. (14,740 gm.) and her height 38½ in. (97.8 cm.). The upper measurements were 21½ in. (53.3 cm.); the lower, 17 in. (43.2 cm.); the circumference of her head, 19¼ in. (48.9 cm.). The child appeared

Fig. 2 and 3.—The twins aged 4 years and 10 months. Leah is smaller but shows no features characteristic of hypothyroidism.



small for her age but well proportioned. She was somewhat timid but friendly. The head was of normal shape and size, the anterior fontanelle closed, but the mother reported that closure had occurred much later than that of her twin. The eyes appeared normal on external inspection, and there was no puffiness of the upper lids. Mild hypertelorism and epicanthic folds were noted, but there was no strabismus or nystagmus. The nose and mouth appeared normal, the lips were thin, the tongue was not protruding. She had 20 teeth and a slight tooth anomaly: her left lower lateral incisor was broad and notched. The neck was normal in outline, the thyroid gland not visible nor palpable. The chest findings were essentially negative; there were no heart murmurs, and the pulse rate was between 84 and 90 after fever had subsided. The abdomen was not protruding, the liver and spleen were not enlarged. The genitalia appeared normal externally. The extremities were anatomically normal except for bilateral incurving of both fourth toes. Her gait was waddling, and she had some difficulty raising her left leg when climbing steps. Neurologic examination was essentially negative. Her skin was of normal texture and color and perspiration normal. Her hair was dark blond, fine and shiny.

Laboratory examinations revealed a white blood cell count of 11,600, with 70% neutrophiles, 27% lymphocytes, 3% monocytes. Hemoglobin was 11.5 gm. per 100 cc. Examination of the cloudy urine showed a specific gravity of 1.016, a trace of albumin, a moderate number of white cells, and many bacteria in the sediment. Urine cultures yielded Aerobacter aerogenes. The nonprotein nitrogen of the blood was 22 mg. per 100 cc. Serum calcium was 9.3; phosphorus, 4.5; cholesterol, 207 mg. per 100 cc. The serum phosphatase was 9.9 Bodansky units.

X-ray examination by Dr. Frederic N. Silverman revealed normal skull findings but skeletal maturation approximating the average for a girl of between 2 and 2½ years (at a chronological age of 4 8/12 years). While the skull development appeared normal for age, it was retarded in comparison with the skull development of the sister. There was irregular epiphyseal mineralization in both femoral heads, more marked on the left than on the right, which was interpreted as cretinoid dysgenesis. The excretory urogram was normal.

Before and during her stay in the hospital, Leah was given 1 grain of thyroid daily. Subsequently the dosage was slowly raised to 2 and 2½ grains (0.13 and 0.16 gm.).

She was reexamined together with her twin sister on March 25, 1954, for determination of blood groups and psychological study. The findings will be discussed later. At that time she was also photographed together with her sister (Figs. 2 and 3). On June 20, 1954, Leah's height had increased to 39¾ in. (101 cm.). She weighed 37 lb. (16,780 gm.), had become more active, and showed definite speech improvement. The mother stated that the twins' "voice and cough" had become indistinguishable. X-ray studies revealed that the irregular mineralization in the femoral capital epiphysis was still present but somewhat less marked. The osseous maturation judged by the phalangeal and metacarpal centers approximated that of a girl between 2½ and 3 years, while the maturation in the carpal centers was that of a girl of 1½ to 2 years. These findings show that Leah's skeletal maturation was still markedly retarded at the age of 5 years, although progress in other respects was satisfactory.

Myra E. H., Leah's twin sister, grew and developed normally. She could sit up at the age of 7 months, walked at 11 months, and began to talk at 1 year. She had whooping cough at the age of eight months and suffered four to five convulsions during febrile episodes. Myra was examined and photographed together with her sister in March, 1954. Her height was then 42¾ in. (118.6 cm.), 4 in. (10.2 cm.) above that of her twin sister. She was a healthy intelligent child, and there were no signs of hypothyroidism. Some slight anatomical anomalies will be mentioned in the discussion of the similarity of the twins. When reexamined on June 20, 1954, her height was 42¾ in. and her weight was 44 lb. (19,960 gm.). X-ray studies showed no abnormalities of the skull and pelvis. The ossification centers at the proximal ends of the femurs were distinctly advanced in comparison with those of her sister. Skeletal maturation was within the normal range for a girl of 5 years.

Although Leah and Myra differed at times greatly in physical and mental traits, they were in all probability monozygotic twins. They were of the same sex, and they had identical blood factors:

		D	C	E	e	S	s	Jk^a	Fy^a	K	k	Le^a	P
Leah	O M	+	+	0	0	+	+	+	0	0	+	+	0
Myra	O M	+	+	0	0	+	+	+	0	0	+	+	0

The parents' blood groups were as follows:

Father	O MN	+	+	+	+	+	+	+	0	0	+	+	0
Mother	A MN	+	+	0	0	+	+	0	+	0	+	+	0

They were so similar after birth that the mother had difficulty distinguishing them. Their skin was of fair complexion with a few nevi but no freckles. Their hair was dark blond, straight, and shiny. Their eyes were of similar shape, both having mild

hypertelorism and epicanthic folds. The iris color was the same, showing a brown center and a bluish-gray periphery. The facial features were very similar, as shown in Figs. 2 and 3. The nose, the labial philtrum, the lips, and the chin were of the same shape, though different in size. The same was true for the ears, the outline of the neck, and the shape of the hands and fingers. The finger and palmprints had similar patterns, but they were not identical. Both girls had a high palate and a mirror-image tooth anomaly. Leah had a broad notched lower lateral incisor on the left, and Myra had a similar lower lateral incisor on the right side. This anomaly was probably due to fusion of two tooth elements. Both twins showed an identical toe anomaly, namely, incurving of the fourth toes on both feet. Both sisters were right-handed, but Leah used the left hand more than Myra.

On March 25, 1954, a psychologic study was made on Leah and Myra. Leah was somewhat fearful and tense during the test and responded better to nonverbal problems than to those requiring the use of words. At a chronological age of 4 years 10 months, her mental age was 4 years 2 months (I. Q.) 86). On the same day Myra was examined and found to be very self-confident; she talked easily and was completely master of the situation. Her mental age was 6 years 8 months (I. Q. 138). She is a child of very superior intelligence.

All the differences between the twins can be explained by Leah's hypothyroidism. Retardation of growth, skeletal and mental maturation, anemia, carotenemia, myxedema, enlargement of the tongue, protrusion of the abdomen, and chronic constipation are features which were at times prominent in the first twin, while her sister developed normally. These symptoms of hypothyroidism were ameliorated by thyroid treatment. Some differences still persist. Among them are retardation of growth, skeletal maturation, and mental development. It is of interest that Leah's mental age was only slightly retarded for a hypothyroid child whose treatment was discontinued at times because of irritability and sleeplessness. This relative success can be attributed in part to the good genetic endowment of the twins, which was manifested by Myra's intelligence quotient of 138. Leah was also constantly stimulated and taught by her twin, who was a friendly and encouraging playmate to her smaller sister. The care and understanding of the parents undoubtedly contributed to Leah's achievements.

Without Myra as a "control," Leah's hypothyroidism could be interpreted as a trait directly inherited from her hypothyroid mother. This explanation is not acceptable, since Leah and Myra had the same genetic constitution but only one twin was affected. It was due, therefore, to nongenetic factors that one twin developed the disease while the other was spared.

Monozygotic twins with discordant hypothyroidism have been described by Harnack [1] and by Grebe.[2] Harnack's case is of great interest because the mother of the twins developed goiter and irritability during the second month of her twin pregnancy. She lost weight and developed subsequently typical hyperthyroidism. Harnack believed that maternal hyperthyroidism during pregnancy may lead to hypothyroidism of the child in utero and reported that in 13 cases of cretinism observed by him maternal hyperthyroidism was present in three instances. In contrast to Harnack's case, the mother of our twins had hypothyroidism of long standing, but it must be emphasized that she took 3 grains of thyroid throughout pregnancy, which could have resulted at times in an excess of thyroid hormone.

Dissimilarity of monozygotic twins attributable to pituitary disturbances in one twin has been repeatedly observed. Komai and Fukuoka [3] described a pair of twins who were very similar until the age of 5 years, when one of the brothers developed diabetes insipidus and began to show retardation in longitudinal growth and weight increase. Lewis [4] reported a pair of male twins who were almost indistinguishable until puberty, when, following a head injury, one of the twins began to grow taller than his brother and developed acromegaloid features. Lüth [5] observed three pairs of uniovular twins with discordance in growth and sexual maturation attributable to pituitary differences.

Dissimilarity of monozygotic twins may date back to early nongenetic deviations of metabolic processes or embryonic organizers. Grebe [2] described a pair of such twins show-

ing remarkable differences. One twin was a dwarf with a generalized skeletal disorder who did not learn to talk and walk until the age of 10 years. His "identical" twin showed relatively normal growth and skeletal development, with an iris coloboma as the only developmental anomaly.

It is not generally known that the development of monozygotic twins can be severely modified by prenatal or postnatal nongenetic factors and that striking dissimilarities may result from such environmental influences.

In 1935 Faxén [6] reported hypothyroidism in one of twins who were probably monozygotic. However, the author did not consider them as identical because, he thought, "It is hardly possible that only one of the two foetuses from the same ovum could be born with a defect that entailed a radical change in both the psychic and bodily development of the individual." This concept, which is still widely accepted, has been refuted by recent twin studies backed by blood-group identification.

Observations of uniovular twins may be of great value in etiologic studies of many disorders and diseases of childhood, but it should be emphasized that such twins sometimes become very dissimilar if the development of one of the twins is modified by abnormal environmental influences.

SUMMARY

Hypothyroidism in one of monozygotic twins resulted in retarded growth and development. The twin sister remained unaffected and showed excellent mental development and normal growth.

Dr. Philip C. Elliott, Nashville, Tenn., supplied the early case history of the twins; Dr. Philip Levine, Ortho Research Foundation, Raritan, N. J., determined the blood factors, and Mrs. Emma K. Fischer did the psychological study.

REFERENCES

1. von Harnack, G. A.: Eineiige Zwillinge mit diskordanter Hypothyreose, Arch. Kinderh. **146**: 60, 1953.

2. Grebe, H.: Diskordanzursachen bei erbgleichen Zwillingen, Acta genet. med. et Gemellol. **1**:89, 1952.

3. Komai, T., and Fukuoka, G.: Postnatal Growth Disparity in Monozygotic Twins, J. Hered. **25**:423, 1934.

4. Lewis, A. J.: A Case of Apparent Dissimilarity of Monozygotic Twins, Ann. Eugenics **7**: 58, 1936.

5. Lüth, K. F.: Endokrine Störungen bei eineiigen Zwillingen, Ztschr. menschl. Vererb.-u. Konstitutionslehre **21**:55, 1937.

6. Faxén, N.: Hypothyroidism in One of Twins, Acta pædiat. **17**:565, 1935.

SALICYLATE POISONING

F. H. HARVIE, M.D., Philadelphia
and
R. B. SINGER, M.D., Boston

SALICYLATES are now among the commoner causes of poisoning in small children, due either to overdosage during treatment of infections or to accidental ingestion. Methyl salicylate (oil of wintergreen) is especially dangerous because of its appetizing odor and the ease with which a large dose can be ingested. One teaspoon is about equivalent in salicylate content to 12 ordinary acetylsalicylic acid tablets and much easier to swallow. Since methyl salicylate locally is of questionable value therapeutically, it would be best to avoid its use in homes where there are small children. Lower degrees of acetylsalicylic acid poisoning in infants are probably commoner than is realized, due to overdosage.

A general concept of salicylate poisoning can be developed from clinical and experimental data now available, the main outline of which is as follows: In the previously healthy person the first effect of ingestion or injection is hyperventilation. As a result, CO_2 is blown off in excess, the plasma CO_2 pressure and CO_2 content fall, and the pH rises. If the dose has been large, a primary metabolic acidosis is soon superimposed on the initial respiratory alkalosis. It is in this mixed stage that diagnosis may be very difficult by ordinarily available laboratory methods, and incomplete diagnosis may, in turn, lead to unwise therapeutic efforts. Additional clinical features unrelated to acid-base disturbance are presumably due to other effects of the salicylate ion. Large doses first stimulate, then depress, the central nervous system, and most of the alarming features seem to be due to these central effects. Excitement, disorientation, convulsions, stupor, and respiratory failure may all appear. Death, if it occurs, seems to be due most frequently to depression of the respiratory center. Many of the other features may also be central in origin, such as headache, tinnitus, deafness, vertigo, and hyperpnea. Vomiting may be due to central as well as local irritation. It may follow intravenous or rectal administration, with no drug being found in the gastric contents.[1] Although the general outline is fairly well established, many features are still obscure.

The following cases of salicylate poisoning demonstrate the value of a little-used method for studying acid-base disturbances which is particularly applicable to infants. In addition, the first patient offered an opportunity to follow the effects of poisoning from an early stage and hence to compare these with the general outline above. The second patient illustrates some of the possible difficulties in diagnosis and treatment.

METHODS

All determinations were made on heparinized whole capillary blood obtained by heel puncture. Prior to puncture the foot is immersed in warm water or wrapped in warm wet towels for a few minutes. A moderately wide and deep puncture is made with a sharp-pointed scalpel blade. The initial vascular spasm following puncture will subside in one-half to one minute if no squeezing is used, and a free flow of blood is usually obtained without excessive manipulation. The drops are allowed to fall on a hollowed-out rubber tip attached to a 2 ml. syringe containing 0.05 ml. of heparin-saline solution and about 0.3 ml. of mercury. The brief exposure to air before each drop is

Present address, 501 Boylston St. (Dr. Singer).

This work was aided by grants from the American Philosophical Society and the Life Insurance Medical Research Fund.

From the Departments of Pediatrics, Physiological Chemistry, and Research Medicine, School of Medicine, University of Pennsylvania, and the Hospital of the University of Pennsylvania.

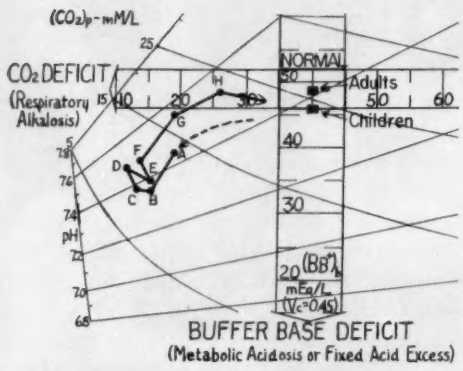


Fig. 1.—Acid-base pathway in Case 1, methyl salicylate intoxication in a 4-year-old boy. The main horizontal scale represents the calculated CO_2 pressure, PCO_2, in millimeters of mercury, the main vertical scale the calculated whole blood buffer base $(BB^-)_b$, in mEq./L. The slanting curved lines with scale at upper left refer to the plasma CO_2 concentration $(CO_2)_P$, in mM./L. (calculated from the observed whole blood CO_2 concentration). The slanting straight lines with scale at lower left refer to plasma or whole blood pH. Note the location of the points generally on the alkaline side of the diagonal line, pH 7.4. If alkali therapy had not been employed, points B to F would have been displaced downward, with lower values for buffer base and pH (more severe buffer base deficit or metabolic acidosis). Data for this case are in the Table.

drawn into the syringe has been shown not to alter the pH or CO_2 content significantly.* As much as 1.5 ml. may be obtained from one puncture.

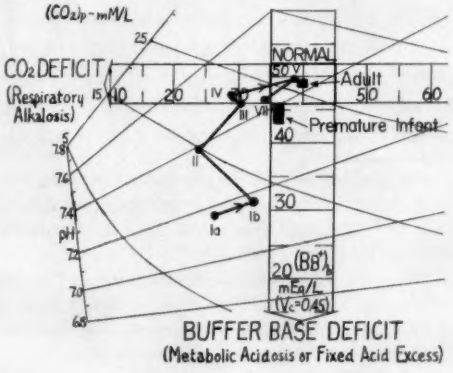
The hematocrit value, whole blood CO_2 content, and colorimetric pH at 37 C. were determined by a modification of the microtechnic of Shock and Hastings.† Hemoglobin was measured in a Klett-Summerson photometer standardized with copper ammonium sulfate by the method of Drabkin.[4] On some samples the excess blood was centrifuged anaerobically and the plasma analyzed for chloride by the Van Slyke and Hiller modification of the Sendroy iodate method [5] and for sodium on an internal standard flame photometer.[2]

From the pH, whole blood CO_2, and hematocrit (or hemoglobin) values, the plasma CO_2 content, CO_2 pressure, and buffer base, $(BB^-)_b$, concentration of whole blood were calculated from the nomogram of Singer and Hastings.[6] Buffer base may be defined as the "base" or cation equivalent to the sum of all buffer anions (in blood, chiefly bicarbonate, hemoglobin, and plasma protein anions), an amount that is therefore available for the neutralization of excess invading acids. For purposes of clinical study it has certain advantages over the usual determinations of plasma CO_2 concentration or CO_2-combining power.[6] The normal buffer base for children has been tentatively taken as 46 ± 3 mEq. per liter.

Cutaneous blood collected as above is essentially the same as arterial blood in its acid-base properties. It is a much better index of the respiratory factor in any acid-base disturbance than is peripheral venous blood. The calculated CO_2 pressure of arterial or cutaneous blood, unlike that of venous blood, closely approximates the CO_2 pressure of alveolar air and is not subject to errors due to stasis or other changes in local blood flow. The collection of blood from the heel as described above may require several minutes, tending to minimize the effects of breath-holding and straining on the CO_2 pressure.

Of the four variables, pH, CO_2 content, CO_2 pressure, and buffer base concentration in oxygenated blood of a given cell volume, only two are independent. That is, if values for two of them are obtained by any means, values of the other two are fixed by their interrelationship. Although it is customary first to determine pH and CO_2 content by

Fig. 2.—Acid-base pathway in Case 2, acetylsalicylic acid intoxication, complicated by dehydration hyperosmolarity, in a 2-month-old infant. The numbers on the points indicate the serial day of hospital observation. The first two points are atypical of salicylate intoxication because the CO_2 pressure is not markedly depressed. Data for this case are in the Table; for additional explanation, see text and caption for Figure 1.



* Singer, R. B.: Unpublished observations.

† References 2 and 3.

analysis, from a physiologic and clinical standpoint it is preferable to regard the CO_2 pressure (a measure of the respiratory factor) and the buffer base (a measure of the metabolic or electrolyte factors) as the "primary" determinants of the acid-base equilibrium. For plotting the data, a specially designed diagram [7] has been used, on which a single point represents the simultaneously occurring values of the four variables just mentioned. For this purpose the CO_2 pressure and buffer base concentration for a standard hematocrit value of 45% have been taken from the nomogram [6] for each set of determined values, as shown in Figures 1 and 2. A standard rather than the actual hematocrit value is used because a slightly different buffer base scale would be needed for each different cell volume.

Acid-Base Data in Three Cases of Salicylate Poisoning

		Whole Blood						Plasma		Alkali Therapy, $NaHCO_3$ Given, mEq./L.†
	Position on Diagram	HCT., %	pH at 37 C.	CO_2 Whole Blood, mM./L.	PCO_2, Mm. Hg*	Buffer Base, mEq./L.*	BUN, Mg./ 100 Cc.	Na, mEq./L.	Cl, mEq./L.	
Normal child, 3 mo.-10 yr.	..	30-47	7.33-7.47	18-24	32-46	43-49	5-20	134-148	98-106	.....
Normal man	..	40-50	7.35-7.45	20-24	35-45	46-52	...	...	...	.....
Case 1, J. A., boy, 4 yr., 13.5 kg., methyl salicylate poisoning										
Hr. After Salicyl.										
5	A	44	7.44	10.6	18	38.5	..	...	94‡	.....
19	B	42	7.33	7.3	16	32.0	..	...	...	12 I.V.
22	C	41	7.35	6.6	14	31.5	..	...	...	.....
24	D	40	7.50	7.7	12	35.5	..	...	...	.....
27	E	38	7.39	7.9	15	32.5	..	...	...	30 I.V.
41	F	36	7.51	8.8	13	36.0	..	...	96‡	30 I.V.
51	G	34	7.57	14.9	19	42.5	..	...	...	8 P.O.
66	H	35	7.54	17.8	26	46.5	..	...	...	.....
Case 2, L. H., boy, 2 mo., 3.0 kg., acetylsalicylic acid poisoning										
Day										
1, 8:00 a. m.	..	..	....	5.4‡	..	....	..	...	129‡	.....
1, 12 noon	Ia	30	7.17	8.8	25	27.5	..	170	144	.....
1, 5:00 p. m.	Ib	26	7.18	11.8	32	30.0	..	...	135	9 I.V.§
2	II	23	7.30	13.8	24	35.5	41‡	169	129	13.5 I.V.
3	III	29	7.47	19.0	29	43.5	..	152	120	.....
4	IV	31	7.49	18.4	29	47.0	10‡	146	...	.....
5	V	32	7.43	23.3	39	48.0	..	...	116	.....
7	VII	38	7.45	19.9	33	46.0	..	149	114	.....
Case 3, F. P., boy, 11 mo., 10.4 kg., sodium salicylate poisoning										
Day 2	..	..	7.44	8.4	14	34.0	..	...	...	.....

* Calculated from other acid-base data.
† The amount of $NaHCO_3$ in the last column refers to the amount given up to the time of sampling and since the previous sampling.
‡ Determinations on venous sample.
§ 30 cc. of citrated blood given at this time.

REPORT OF CASES

CASE 1.—J. A., a 4-year-old Negro boy weighing 13.5 kg., was admitted to the pediatric service of the Hospital of the University of Pennsylvania on Oct. 28, 1949. At 5 p. m. that day he had swallowed about 2 or 3 tablespoons (30 to 45 cc.) of methyl salicylate, which had been prescribed for his grandmother to rub on her chest. Soon afterward he began to vomit violently and continued to do so after his stomach was empty. The vomitus had an odor of wintergreen. He "acted silly," complained of headache, and said he could not see. He became very weak and sweated profusely. He reached the hospital at 8:30 p. m., and there his stomach was immediately emptied by lavage; no wintergreen odor was noticed. On admission he was somewhat lethargic but responsive and cooperative. The respirations were 24 per minute, with apparently mild but definite increase in depth. He did not appear particularly ill. His rectal temperature was normal on admission and did not exceed 100.6 F. at any time. The clinical course was marked by progressive increase in the depth and rate of respirations, with nausea, vomiting, irritability, agitation, and disorientation. These features reached their peak in about 24 hours, at which time he appeared to be seriously ill. Treatment was begun the first evening with 5% dextrose solution by intravenous drip with additions as shown in the Table.

The clinical course may be discussed in relation to the acid-base changes as plotted on the special

diagram (Fig. 1). The original data are listed in the Table. The first point, A, five hours after taking the drug, shows a low CO_2 content of 10.6 mM./L. and a high normal pH of 7.44. The buffer base is somewhat reduced at 38 mEq./L., but the very low CO_2 pressure of 18 mm. of mercury is indicative of severe hyperventilation. The low CO_2 content (10.6 mM./L.) is produced partly by the primary hyperventilation and partly by some degree of metabolic acidosis in this early stage of intoxication. Points B to E, obtained at 19 to 27 hours after poisoning, show still lower CO_2 pressures and a further decrease of the buffer base in spite of sodium bicarbonate given intravenously. The acid-base disturbance here consisted of a mixed primary CO_2 deficit and primary buffer-base deficit. Calculated on the basis of extracellular fluid (20% of body weight) with no allowance for removal of extracellular sodium into cells or through the kidneys, the initial dose of 12 mEq. of bicarbonate (0.9 mEq. per kg. of body weight) (1 gm., or 70 ml. of M/6 solution) would have been expected to raise the buffer base by about 4 or 5 mEq./L. in a nonacidotic child, whereas the level actually dropped by 6 mEq./L. The second dose, of 30 mEq. (2.2 mEq. per kg.) (180 ml. of M/6 solution), given between D and E, produced a small rise of 4 mEq./L. rather than a theoretically predicted rise of 11 mEq./L. At the same time continued hyperventilation had further depressed the CO_2 pressure to 11.5 mm., in the range of the lowest figures reported during maximal voluntary hyperventilation. Undoubtedly still lower values for buffer base, pH, and CO_2 content would have been found at this time if no alkali had been given. This course of events was considered as probably due for the most part to continued accumulation of organic acids, plus some loss by renal excretion of sodium and some expansion of extracellular volume as indicated by the fall in hematocrit value. The urinary pH at this time was 4.5 with nitrazine paper. From the data it was estimated that the apparent reduction in buffer base, due to acid accumulation, had been proceeding at a rate of approximately 2.5 mEq. per hour (see under Comment). Further dosage of bicarbonate was given at this rate, between points E and F. This interval, characterized by return of the buffer base toward normal, coincided with marked clinical improvement of the patient. By the third hospital day he was alert and able to take fluids orally. At the time of discharge, on the fourth day, he appeared well, although the respirations were still recognizably deeper than normal and the CO_2 pressure and content were still low. Points G and H again correspond to a condition of primary CO_2 deficit due to hyperventilation, with high pH, low CO_2 content, and normal buffer base. No signs of tetany were observed.

CASE 2.—L. H., a 2-month-old Negro boy, was admitted to the pediatric service of the Hospital of the University of Pennsylvania on Jan. 17, 1951, with a history of nasal discharge for one month, some difficulty with feeding, and a cough for two weeks with occasional vomiting. Three days before admission he became acutely ill, with fever, irritability, and rapid breathing. By a prescription given elsewhere, it was later found that he had received approximately 4 gm. of acetylsalicylic acid in the three days before admission.

The baby was one of twins, with a birth weight of 2,480 gm., and had done well the first month. Because of housing difficulties the baby had been cared for by his grandparents. The history was obtained piecemeal and with great difficulty, and it was not learned until later that he had received several medications during the preceding month, including a variable number of 1¼-grain (75 mg.) acetylsalicylic acid tablets, ranging from two to five each day for three or four weeks, occasional doses of a proprietary laxative (Castoria) and camphorated opium tincture, and several doses of catnip tea in the three days prior to admission.

On admission he appeared acutely ill, with a rectal temperature of 105 F., pulse rate 168, respiration rate 32, weight 3 kg. Nutrition and development were only fair. The skin and mucous membranes were dry. Inspiration was associated with flaring of the nostrils and some sternal retraction. The lungs were clear. The rest of the examination was not remarkable. Initial laboratory studies were as follows: hemoglobin, 11.3 gm.; W. B. C., 20,000 (with N. 47%, L. 46%, M. 7%); urine, acid with a trace of albumin and occasional finely and coarsely granular casts; venous serum CO_2, 5.4 mM./L., and chloride, 129 mEq./L.

Initial treatment was with 0.9% saline and 5% dextrose solution subcutaneously. The first specimen of cutaneous blood was obtained at noon on the day of admission and showed the following values: pH 7.17, whole blood CO_2 8.8 mM./L., calculated buffer base 28 mEq./L., calculated CO_2 pressure 25 mm. Hg, serum chloride 144 mEq./L. The initial interpretation was metabolic acidosis, and 9 mEq. of sodium bicarbonate was given intravenously, followed by a slow drip of 5% dextrose solution and 30 ml. of whole citrated blood. The high serum chloride concentration became known about this time and was thought to be a factor in the acidosis, but the extraordinarily high sodium content of 176 mEq./L. was not known until the following day. In the evening of the first day the baby became critically ill, with slow and uncertain breathing, cyanosis, twitching, and convulsions. He was given oxygen and intravenous calcium gluconate. Within two hours he had improved, the respiratory rate being 56 to 80 without unusual depth, and no further convulsions were seen. It

was not until the second day that the story of acetylsalicylic acid administration was finally elicited. The skin had a thick doughy feel in keeping with his hyperosmolaric dehydration as described by Rapoport,[8] explainable in this case by the baby's small size and loss of water without electrolyte, due to high fever, hyperventilation, and failure of renal osmotic regulation. Hyperventilation was less prominent than in the first case, as indicated by the clinical appearance and the smaller drop in CO_2 pressure. Hartmann[9] has noted that small babies who are very ill may not show much respiratory response to acidosis until the clinical condition improves with treatment. Kety and associates[10] have observed the same sequence in patients with diabetic acidosis.

Subsequent chemical data and treatment are shown in the Table. After another 13.5 mEq. of sodium bicarbonate given on the second day, the buffer base was only slightly below normal at 36 mEq./L., and treatment was continued with 5% dextrose solution alone, with gradual return of the blood chemistry to normal. A multiple-salt solution was added on the fifth day and full milk feedings on the seventh day. The subsequent course was uneventful.

Urine collected on the second and following days showed specific gravities of 1.013, 1.016, and 1.006 on three separate occasions. The urinary pH readings of 5.6 to 6.0 are perhaps not reliable because of improper preservation; however, the value would be more likely to rise than fall after voiding. They were collected at a time when the blood was slightly alkaline. The initial specimen (collection ended the morning of the 19th) showed Na and Cl concentrations of only 92 mEq./L. each at a time when the plasma levels were still very high (Table). Since urine volume was apparently adequate, these findings support the concept of impaired renal functional capacity to maintain a normal plasma osmotic pressure and ionic pattern under the existing circumstances.

CASE 3.—F. P., an 11-month-old white boy, was admitted to the pediatric service of the Hospital of the University of Pennsylvania on Oct. 16, 1949, at 6 p. m. At 8:30 a. m. the same day he had swallowed "at least" nine pills which had been prescribed for an aunt; they were later identified as sodium salicylate. He had vomited a few times during the day and had perspired profusely all day. In the afternoon he became irritable and lethargic and his breathing was heavy. On admission he was mildly lethargic and showed some hyperventilation. The respiratory rate was 28, pulse rate 140. He was afebrile and remained so. Through the night he received 225 cc. of 5% dextrose solution and 275 cc. of 0.9% saline parenterally, and milk orally, which he retained after the first feeding. By the next morning he was much improved and took food satisfactorily, but he remained lethargic and hyperpneic for two days. Only one study was done on cutaneous blood, approximately 26 hours after ingestion of salicylate, with the following results: pH 7.44, whole blood CO_2 8.4 mM./L., calculated buffer base 34 mEq./L., calculated CO_2 pressure 14 mm. Hg. These findings again indicate the presence of primary respiratory alkalosis combined with primary metabolic acidosis.

COMMENT

ABSORPTION AND EXCRETION OF SALICYLATE

Absorption of salicylate begins promptly after ingestion. After a single dose of sodium salicylate given to adults, the plasma level reaches a peak in about one and one-half hours.[11] After administration of acetylsalicylic acid, the peak level is somewhat lower, comes a little later, and falls more slowly. Single doses of acetylsalicylic acid are largely excreted in 15 to 30 hours,[12] although traces may be found in the urine for two or three days. Approximately 70% is excreted in the urine, some in the free form but mostly as salicylurate and in other chemical combinations. Some is lost in sweat; about 20% is oxidized in the tissues. Sodium bicarbonate increases the rate of absorption[12] and excretion ‡ and reduces the plasma levels.[11] Absorption of methyl salicylate is much slower, so that gastric lavage is worth while even several hours after ingestion.[13]

HYPERPNEA

Of all the toxic effects, hyperventilation has been most studied. In infants and children it is the most constant and distressing of the nonlethal effects and adds much confusion to the blood chemical picture. It is now agreed that the hyperventilation is not primarily caused by acidosis. After injection of sodium salicylate into anesthetized cats,[1] respiratory stimulation was immediate. Sodium salicylate had the same hyperpneic effect whether given in water, 5% sodium bicarbonate solution, sodium lactate solution, or 10% calcium gluconate. When sodium bicarbonate was given intravenously to poisoned dogs, there was no immediate effect on the hyperpnea or the blood CO_2 tension, although the serum bicarbonate and pH in-

‡ References 11 and 12.

creased.[14] In this same study, hyperventilation developed following salicylate injection before any change in blood pH.

The hyperventilation appears to be due to a specific pharmacologic action of salicylate in stimulating the respiratory center, but the exact mechanism is still not clear. The respiratory stimulation was not abolished in animals by removal of the carotid bodies or by large doses of atropine. Evidence has been presented to suggest that the effect may be primarily peripheral and mediated through afferent fibers in the vagus nerves.[1]

Kidneys

The renal effects of salicylate poisoning have received rather little attention. In both rats [15] and dogs [14] profuse diuresis is a striking feature. Oliguria is frequently reported in patients, perhaps a later effect due to dehydration. Proteinuria is common. Casts and cells have been reported. The possibility of functional disorders related to loss of base has already been mentioned.[11] Up to four hours after poisoning, rat urine was always alkaline and contained bicarbonate,[15] presumably a reflection of the initial respiratory alkalosis of hyperventilation. Between four and seven hours after poisoning, the urine was acid regardless of the dose, with pH from 6.4 to 6.9. The patients of Spector and McKhann [16] all showed acid urine.

Sweating and Antipyresis

The antipyretic effect of salicylates is said to be mediated through the central nervous system and is prevented by high section of the spinal cord.[13] The effect is entirely due to heat loss by sweating and vasodilation, and there is no reduction of normal body temperature. It has been stated that marked sweating does not occur in the absence of fever,[13] but profuse sweating is a common feature of uncomplicated poisoning, as illustrated by two of the patients reported here. Mild fever was common among poisoned dogs [14] and is frequently mentioned in clinical reports. Our Case 1 reached 100 F. rectally; Case 3 reached 99.2 F. on one occasion.

Hemorrhage

In clinical salicylate poisoning, hemorrhagic features are seen and sometimes appear to have been terminal.[17] Bleeding is believed to be due to vasodilatation plus reduction in prothrombin. The effect of salicylate is similar to that of bishydroxycoumarin (Dicumarol) in reducing prothrombin, and the two drugs complement each other in this respect. Salicylate is a product of alkaline degradation of bishydroxycoumarin,[18] but the exact relationship between the two drug effects is not clear. Prothrombin reduction by salicylates is greater in patients with hepatic cirrhosis, and it is believed to act through the liver in some way. The effect on prothrombin is said to be counteracted by vitamin K, 1 mg. being approximately enough to overcome the effect of 1 gm. of salicylate. §

Ketosis

Ketosis has been reported frequently in children with salicylate poisoning. Young children tend to develop ketosis readily in the course of any infection or in association with starvation or dehydration. However, our Cases 1 and 3 had not been ill previously, and the urines were positive by the Rothera test on the first day. In a 2-year-old child reported by Erganian and associates,[17] with infection as well as poisoning, the base-binding ketones in the blood amounted to 11 mEq. per liter. It is not stated at what stage of the poisoning this determination was done. Ketonuria is apparently often absent in adults with salicylate poisoning.[1] Rabbits given salicylate until they became severely and fatally dyspneic [21] showed no acetonemia. Infants under 7 months of age seem to have little capacity for producing ketone bodies when placed on a ketogenic diet,[22] and in a study of 20 infants under 3 months of age who were vomiting from a variety of causes, only 1 developed significant ketonemia.[23] Similar data for young infants with salicylate poisoning have not been found. Further reference to organic acid accumulation will be found below.

§ References 19 and 20.

Some of the confusion clinically may be caused by fallacies in the commonly used tests for ketones in urine. Salicylates give a violet color with the ferric chloride test, unlike the Burgundy red produced by acetoacetic acid, but confusion is likely when both are present. Ketones will be volatilized off by boiling, whereas salicylates will not. The Rothera test with nitroprusside is much more sensitive to acetoacetic acid than to acetone, so the amount of color produced will depend on the relative amounts of each substance present. Since acetoacetic acid tends to decompose into acetone in voided urine, the test may become weaker as the urine gets older. The test is not entirely specific for acetone bodies, but a positive test is strongly suggestive of their presence. Its specificity can be improved by using a distillate of urine, during which process acetoacetic acid will again decompose to acetone, and the test will be weaker than on the original specimen. A positive test is shown by a permanganate tinge which gradually deepens; a brown color is not positive. Probably the most satisfactory test for acetone bodies is the salicylate aldehyde test of Behre carried out on a distillate of urine.[24] The Benedict test for reducing substances may be slightly positive with salicylates.

Disturbance in Acid-Base Equilibrium

The changes in acid-base balance during salicylate poisoning are of particular interest to pediatricians, since they are most extreme and most confusing in infants and small children. These changes are illustrated by the data on Case 1 above, a child who was well until he ingested methyl salicylate. The early blood chemical data (Table and Fig. 1) confirm the impressions from animal ‖ and clinical ¶ studies that the early stages of poisoning are associated with respiratory alkalosis, characterized by serum pH values in the high normal or alkaline range and low blood CO_2 levels, due to hyperventilation. In Case 1 five hours after poisoning the blood CO_2 tension was already very low, at 18 mm. of mercury, and the CO_2 content down to 10.6 mM./L. The buffer-base value was only about 8 mEq./L. below the average normal, and the pH was 7.44. With milder degrees of poisoning, especially in adults and older children, the acid-base disturbance does not develop beyond this respiratory alkalosis, the diagnosis of which is often missed through lack of pH determinations. In the more severely poisoned patients, probably exacerbated by the presence of infection as well but not necessarily dependent on its presence, the early respiratory alkalosis is soon obscured by superimposition of a true primary metabolic acidosis as shown by marked fall in buffer-base concentration and shift of pH to the acid side of normal. The causes of this acidosis are obscure. Some sodium is probably lost by renal excretion in an effort to correct the initial alkalosis, but this is a rather slow process and cannot produce a primary metabolic acidosis with pH levels on the acid side of normal. Rapoport and Guest [14] suggested that some sodium and potassium loss might be due to renal damage from the drug. Internal shifts of sodium, potassium, and other ions may occur in the body in response to the needs imposed by acidosis or alkalosis.[26] However, the metabolic acidosis of this later and more severe phase of salicylate poisoning is most probably caused by accumulation of organic acid metabolites.[3] Ketosis contributes to the effect in some cases,[17] especially where starvation or dehydration are involved, but is not the only factor.[3] Salicylate ion itself does not play an important part,[17] nor is renal retention of sulfate or phosphate a significant factor. Possibly salicylate has important effects on intracellular metabolism, although data to support such an idea are very meager.[15] The pathogenesis and characteristics of the acid-base disturbances in salicylate poisoning have been discussed in greater detail elsewhere.[3]

Treatment

The patient who has taken a single large dose of salicylate may appear deceptively well when first seen and for a few hours

‖References 1 and 14.

¶ References 1, 3, 16, and 25.

afterwards. Gastric lavage should not be omitted unless it can be clearly established that the dose taken was small. Since sodium bicarbonate enhances absorption of the drug,[12] it should not be used in the lavage water. As noted above, methyl salicylate may be absorbed over several hours, so that even late lavage is indicated. Fluids are needed, parenterally if necessary, to combat the dehydration of vomiting and sweating and to promote renal excretion of the drug. Renal excretion of salicylate is significantly increased as the urine pH rises above 7.# However, the early alkalosis prohibits any attempt to utilize this effect by giving alkali in the initial stages. By the time the most severe phase of the acid-base disturbance is over, the patient is out of danger and alkalinization of the urine is not worth while. Futhermore, hyperventilation is one of the last features to disappear, and hence the danger of alkalosis persists. Added carbohydrate should help to prevent the ketosis of starvation. The survival rates for salicylate-poisoned rats were significantly improved by giving them extra dextrose for one or two days before injection of the drug.[15] If convulsions appear, anticonvulsant drugs should probably be avoided because of the dangerous degree of central depression which may result. Barbiturates or paraldehyde greatly augment the depressant effect of salicylates in animals, and morphine caused convulsions in poisoned dogs.[14] Since the convulsions may be due to cerebral anoxia, oxygen should be tried first. Alkalotic tetany responds, at least temporarily, to use of carbon dioxide inhalation, perhaps to calcium gluconate intravenously as well. Carbon dioxide should be used cautiously, in concentrations not higher than 5%. Routine treatment should include the use of vitamin K in large doses, ascorbic acid, and plasma albumin or whole blood for shock.

Because of the confusingly mixed nature of the acid-base disturbance, blood chemical determinations need to be as complete as possible if misinterpretation is to be avoided and need frequent repetition. Blood pH determinations are almost obligatory. Knowledge of the buffer base will help greatly in assessing the relative significance of the low blood CO_2 and elevated pH of the early alkalotic stage. The use of depressant drugs to reduce the hyperventilation is probably contraindicated, as noted above. The later phase of metabolic acidosis, if it develops, can be ameliorated by use of alkali. However, in this and other conditions associated with disporportionate hyperventilation, e. g., some cases of diabetic acidosis during recovery,[10] the dose of alkali should be less than that calculated to restore the buffer base or CO_2 content to normal. If frequent measurements of pH and CO_2 content are available, therapy can be readily adjusted to changing circumstances, aided greatly by calculation of the buffer base and CO_2 pressure. In calculation of the dosage of alkali to elevate the plasma CO_2, a volume factor of one-fifth of body weight (extracellular fluid volume) or one-third (to allow for limited intracellular penetration) will be safer than one of two-thirds body weight, as commonly used. Furthermore, in most situations a small dose will be sufficient to bring the child out of danger and permit reassessment. The reader is referred elsewhere for a fuller discussion of this problem.[9]

In the management of Case 1 above, an alternative method was used to estimate the dose of alkali. In the first 24 hours (Fig. 1, Points A to E) the buffer base fell by 6 mEq./L. in spite of the administration of 42 mEq. of sodium bicarbonate. Assuming an extracellular fluid volume of 2.7 liters (one-fifth body weight), this would indicate an accumulation of at least 58 mEq. of fixed acid per 24 hours ($2.7 \times 6 + 42$). This is a minimum, since there is no way at present of estimating acid accumulation or buffering effects inside tissue cells. It is independent of the effects of renal excretion of acid or administered alkali. Assuming a constant rate of acid accumulation, it was estimated that about 30 mEq. of alkali would be needed during the next 12 hours to maintain the buffer base at the same level. Since the pH

References 11 and 12.

was already normal and the buffer base not seriously depressed, this dose was given by slow intravenous drip of isotonic sodium bicarbonate solution. It will be seen (Table, Fig. 1, Points E to F) that the pH was raised well above normal and the buffer base rose slightly during this period, suggesting that the rate of acid accumulation must have slowed down considerably coincident with clinical improvement of the patient. When the acid-base composition of the intake is known, this method of estimating alkali requirement could be used for patients with other types of continuing metabolic acidosis. The dose given to this patient may be compared to that which might have been calculated from the plasma CO_2 deficit using a volume factor of two-thirds body weight. Assuming a deficit at Point E of 14 mM./L., the dose of sodium bicarbonate would have been about four times the amount actually given, with tetany or respiratory depression as possible results. If complete blood chemical studies are not available, it would seem that the risk from acidosis for infants with salicylate poisoning is often less than that from overtreatment with alkali.

It has been reported that salicylate can be removed from the blood much more rapidly through an "artificial kidney" device than by the patient's own kidneys. This method of treatment has been recommended for patients who are gravely ill.[27]

The method of studying acid-base disturbances which was used for these patients has been invaluable to us in the management of patients with obscure or otherwise difficult types of disturbance. It is readily applicable to the smallest infants and to those most severely ill. It requires very small amounts of blood, which can be collected without disturbing the patient or interfering with treatment, and it gives information which otherwise must often be guessed at. By virtue of a clear separation of the respiratory from the metabolic and renal factors, treatment is placed on a rational basis. In Case 2 additional determinations of serum sodium and chloride were needed to bring out the severe degree of hyperosmolarity which was present. Even so, the knowledge that the buffer base was only slightly low and adherence to the general precaution in treating babies not to attempt full correction at one time to a theoretically normal blood electrolyte pattern would have prevented serious overtreatment. Continued administration of 5% dextrose in water would have permitted eventual correction.

SUMMARY

A method of studying acid-base disturbances has been presented which permits the separation of respiratory effects from metabolic and renal factors. It is particularly applicable to infants.

The value of this method has been illustrated in relation to three cases of salicylate poisoning.

Salicylate poisoning has been discussed with respect to pharmacology, clinical features, and treatment. Hyperpnea, some features of the acid-base disturbance, and the use of alkali have been particularly stressed.

Dr. J. Russell Elkinton, of the Department of Medicine, did the sodium analyses and the urine chloride determinations. The observed sodium and chloride concentrations were corrected for the amounts contained in the heparin-saline solution with which the blood samples were originally mixed.

REFERENCES

1. Graham, J. D. P., and Parker, W. A.: The Toxic Manifestations of Sodium Salicylate Therapy, Quart. J. Med. **17**:153, 1948.

2. Shock, N. W., and Hastings, A. B.: Studies of the Acid-Base Balance of the Blood: I. A Microtechnique for the Determination of the Acid-Base Balance of the Blood, J. Biol. Chem. **104**:565, 1934.

3. Singer, R. B.: The Acid-Base Disturbance in Salicylate Intoxication, Medicine **33**:1, 1954.

4. Drabkin, D. L.: The Standardization of Hemoglobin Measurement, Am. J. M. Sc. **215**:110, 1948.

5. Van Slyke, D. D., and Hiller, A.: Application of Sendroy's Iodometric Chloride Titration to Protein-Containing Fluids, J. Biol. Chem. **167**:107, 1947.

6. Singer, R. B., and Hastings, A. B.: An Improved Clinical Method for the Estimation of Disturbances of the Acid-Base Balance of Human Blood, Medicine **27**:223, 1948.

7. Singer, R. B.: A New Diagram for the Visualization and Interpretation of Acid-Base Changes, Am. J. M. Sc. **221**:199, 1951.

8. Rapoport, S.: Hyperosmolarity and Hyperelectrolytemia in Pathologic Conditions of Childhood, Am. J. Dis. Child. **74**:682, 1947.

9. Hartmann, A. F., and Erganian, J.: Treatment of Diabetic Acidosis, J. Pediat. **31**:274, 1947.

10. Kety, S. S.; Polis, B. D.; Nadler, C. S., and Schmidt, C. F.: The Blood Flow and Oxygen Consumption of the Human Brain in Diabetic Acidosis and Coma, J. Clin. Invest. **27**:500, 1948.

11. Smith, P. K.; Gleason, H. L.; Stoll, C. G., and Ogorzalek, S.: Studies on the Pharmacology of Salicylates, J. Pharmacol. & Exper. Therap. **87**:237, 1946.

12. Lester, D.; Lolli, G., and Greenberg, L. A.: The Fate of Acetylsalicylic Acid, J. Pharmacol & Exper. Therap. **87**:329, 1946.

13. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941, p. 229.

14. Rapoport, S., and Guest, G. M.: The Effect of Salicylates on the Electrolyte Structure of the Blood Plasma: I. Respiratory Alkalosis in Monkeys and Dogs After Sodium and Methyl Salicylate; the Influence of Hypnotic Drugs and of Sodium Bicarbonate on Salicylate Poisoning, J. Clin. Invest. **24**:759, 1945.

15. Lutwak-Mann, C.: The Effects of Salicylate and Cinchophen on Enzymes and Metabolic Processes, Biochem. J. **36**:706, 1942.

16. Spector, S., and McKhann, C. F.: Respiratory Acidosis and Alkalosis in Children, J. Pediat. **32**:227, 1948.

17. Erganian, J. A.; Forbes, G. B., and Case, D. M.: Salicylate Intoxication in the Infant and Young Child: Report of 13 Cases, J. Pediat. **30**:129, 1947.

18. Stahmann, M. A.; Huebner, C. F., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: V. Identification and Synthesis of the Hemorrhagic Agent, J. Biol. Chem. **138**:513, 1941.

19. Link, K. P.; Overman, R. S.; Sullivan, W. R.; Huebner, C. F., and Schell, L. D.: Studies on Hemorrhagic Sweet Clover Disease: Hypoprothrombinemia in Rats Induced by Salicylic Acid, J. Biol. Chem. **147**:463, 1943.

20. Krantz, J. C., Jr., and Carr, C. J.: The Pharmacologic Principles of Medical Practice, Ed. 2, Baltimore, Williams & Wilkins Company, 1951.

21. Myers, H. B., and Ferguson, C.: The Effect of Salicylate Administration on the Acetone Body Content of the Blood, J. Pharmacol. & Exper. Therap. **35**:313, 1929.

22. Heyman, W.: Metabolism Studies on Age Disposition to Ketosis in Human Beings, J. Pediat. **12**:21, 1938.

23. Gray, C. H.: Ketonemia in Infancy, Lancet **2**:1017, 1937.

24. Hawk, P. B.; Oser, B. L., and Summerson, W. H.: Practical Physiological Chemistry, Ed. 12, Philadelphia, The Blakiston Company, 1947, pp. 772-3.

25. Farber, H. R.; Yiengst, M. J., and Shock, N. W.: The Effect of Therapeutic Doses of Aspirin on the Acid-Base Balance of the Blood in Normal Adults, Am. J. M. Sc. **217**:256, 1949.

26. Gamble, J. L.: Companionship of Water and Electrolytes in the Organization of Body Fluids, Lane Medical Lectures, Stanford, Calif., Stanford University Press, 1951.

27. Doolan, P. D.; Walsh, W. P.; Kyle, L. H., and Wishinsky, H.: Acetylsalicylic Acid Intoxication: Proposed Method of Treatment, J. A. M. A. **146**:105, 1951.

AMINO-ACIDURIA, HYPOPHOSPHATEMIA, AND RICKETS IN LEAD POISONING

Study of a Case

J. JULIAN CHISOLM Jr., M.D.; HELEN C. HARRISON, Ph.D., Baltimore; WALTER R. EBERLEIN, M.D., Boston, and HAROLD E. HARRISON, M.D., Baltimore

With the Technical Assistance of Flo C. Mohr, A.B.

THE CASE is presented of a child with lead poisoning who developed biochemical disturbances similar to those seen in the congenital metabolic defect known as the de Toni-Fanconi syndrome. The most important aspects of the disturbance demonstrated in the child were amino-aciduria, glycosuria, hypophosphatemia, and the skeletal changes of acute rickets.

The occurrence of transient glycosuria and of anatomic renal tubular lesions in human lead poisoning has long been known, although the nature of the biochemical disturbance involved remains obscure. This case provides new information on this point and may indicate a new avenue of approach in the study of lead poisoning.

Recently, Wilson and co-workers [1] reported coincident glycosuria and gross amino-aciduria in a child with lead poisoning. In their case, however, there was no roentgenologic evidence of rickets and no emphasis was laid upon changes in serum phosphorus concentration. In 1938, Caffey [2] reported the occurrence of active rickets in a child with lead poisoning. In his case glycosuria was present and the x-ray findings were quite similar to those in the present case; however, few biochemical data were included in the report. To our knowledge, no other case of lead poisoning demonstrating the constellation of amino-aciduria, glycosuria, hypophosphatemia, and the skeletal changes of acute rickets has been reported.

Present address: Children's Hospital, Philadelphia (Dr. Eberlein).

From the Harriet Lane Home for Invalid Children and the Department of Pediatrics of The Johns Hopkins University Medical School.

This investigation was supported by grants from the Lead Industries Association, New York, and from the Playtex Park Research Institute.

REPORT OF A CASE

D. N. (HLH #A99820), a 33-month-old white boy, was first admitted to the Harriet Lane Home on Jan. 26, 1953, with the presenting complaints of severe vomiting, drowsiness and strabismus of 5 days' duration, and a history of pica for painted wood chips of 20 months' duration.

Both parents and one half-sister (the only other offspring of either parent) were living and well. There was no history suggestive of rickets or of renal or hepatic disease in the family.

Birth, the neonatal period, and motor development had been normal. Since the age of 2 years, however, moderate retardation in language and personal-social development had become apparent. The patient had received fortified evaporated milk exclusively since birth; no other vitamin D supplement had been given after the age of 4 months. Dietary intake was otherwise adequate. The remainder of the past history was noncontributory.

Approximately 8 to 10 weeks prior to admission the mother first noted that the child was becoming "weak." This "weakness" manifested itself as anorexia, apathy, refusal to play, and a whining irritability. His symptoms had progressed, insidiously, to the point of general debility at the time of admission. During the five weeks prior to admission he had three acute episodes (each lasting about one week), which consisted of severe vomiting, complete anorexia, listlessness, and strabismus. From the first two bouts he recovered spontaneously at home. During the third, however, he became quite lethargic and for this reason was referred to the hospital. At this time the history of pica was first obtained.

On admission (temperature, 37.2 C.; pulse rate, 122; respiration rate, 24; B. P. 105/65), physical examination revealed a pallid, chronically ill, lethargic child, who could be aroused with difficulty. He was hyperirritable when aroused. There were no deformities or other physical findings suggestive of rickets. A marked bilateral sixth cranial nerve weakness was present. Neurological examination was otherwise within normal limits, as were the remainder of the physical findings.

The pertinent admission laboratory data * confirming the clinical impression of plumbism with encephalopathy and anemia were as follows:

X-rays: Skull showed marked separation of the sutures. Long bones showed generalized osteoporosis, but no lines of increased density at their metaphyseal ends.

Lumbar puncture: Opening pressure, greater than 600 mm. CSF; closing pressure, 400 mm. CSF; cells, 8 mononuclears; CSF protein, 140 mg./100 cc.

Urinalysis: Albumin, negative; Benedict's qualitative test, 2+; microscopic study, negative; qualitative test for coproporphyrin, strongly positive.

Blood studies: Hemoglobin, 8.2 gm.; RBC, 4,600,000; hematocrit value, 33%; reticulocytes, 2.1%; MCV, 72 cu.μ; MCHb, 17μγ, MCHbC, 24%; frequent basophilic stippling of erythrocytes.

Urine and blood lead: Urine, 2.57 mg. lead per liter; total 12-hour output, 0.411 mg. lead. Blood, 0.41 mg. lead/100 gm. whole blood.

The child's initial precarious clinical status responded satisfactorily to the administration of a total of 5 gm. of edathamil calcium-disodium † (CaEDTA) given parenterally over a five-day period. Lethargy disappeared after 24 hours of therapy; strabismus and increased spinal fluid pressure, after 48 hours. Improvement in appetite and reduction in irritability were more gradual. The anemia responded to a four week course of oral iron therapy.

When the boy was last seen (as an outpatient), after eight months of observation, there was no evidence of further lead ingestion and the hematological picture was normal. Despite considerable early improvement in mental and emotional status, moderately severe mental retardation was still evident.

On the fourth day of edathamil calcium-disodium therapy determinations of serum calcium, phosphorus, and alkaline phosphatase activity were made, with the following results: calcium, 10.1 mg. per 100 cc.; phosphorus, 2.0 mg. per 100 cc.; alkaline phosphatase activity, 9.2 Bodansky units. Because of hypophosphatemia and roentgenologic evidence of defective ossification, metabolic studies were undertaken.

METABOLIC STUDIES

Method of Study.—Following recovery from the acute phase of his encephalopathy, the patient was placed upon regular house diet with whole cow's milk. No vitamin D supplement was given. This regimen was maintained throughout the entire 66 days of hospitalization. The diet was taken with progressively improving appetite. Upon discharge, evaporated milk was resumed at home in amounts providing a daily intake of about 400 units of vitamin D during the remaining 132 days of the study. No other form of vitamin D was given at home. A course of oral citrate therapy was administered in the hospital and resumed at home upon discharge.

The patient's course was followed with x-ray studies of the long bones and serial determinations of the concentrations of serum calcium, phosphorus, alkaline phosphatase activity, citrate, sodium, potassium, carbon-dioxide-combining power, and whole blood NPN and lead. Pooled three-day stool collections were made for the determination of fecal lead output. To obtain quantitative collections of urine for the determination of 24-hour outputs of calcium, phosphorus, citrate, creatinine, lead, and amino acids, a metabolism frame was used. Toluene was used as a preservative when citrate and amino acids were determined, and the specimens for amino acid determination were refrigerated in an ice-water bath during collection. Lead-free collection equipment (nitric acid washed) was used when collecting specimens for lead analysis.

The methods of analysis of blood and urine were as follows: calcium, Kramer and Tisdall [3]; phosphorus, Fiske and Subbarow [4]; citrate, Natelson, Pincus and Lugovoy [5]; alkaline phosphate activity, Bodansky [6]; urinary amino acids, a modification of the chromatographic technique of McFarren and Mills [7] on unhydrolysed urine. Benedict's qualitative reaction only was used to detect reducing substance in the 24-hour urine samples. Urine and stool samples were dry-ashed and their lead ‡ content determined by a modification of the method of Snyder.[8] Other serum analyses were performed by the clinical chemistry laboratory.

Therapy.—When the picture of hypophosphatemia, amino-aciduria, and rickets was recognized, the effects of citrate administration were studied for the following reasons: Citrate is known to be effective in the healing of rickets, although serum phosphorus concentrations may remain low.[9] Recently, Bickel and Smellie [10] reported that treatment with potassium chloride and sodium citrate-citric acid in combination with vitamin D

* Two samples of the paint chewed by the patient contained 15 and 30% lead, respectively, upon analysis.

† The edathamil calcium-disodium used in the treatment of this case was kindly supplied by Riker Laboratories, Inc.

‡ Dr. Emanuel Kaplan, Chief, Division of Chemistry, Bureau of Laboratories, Baltimore City Health Department, made the multiple determinations of blood lead content.

resulted in the gradual diminution and eventual disappearance of amino-aciduria and glycosuria and in the healing of the skeletal changes of rickets in patients with the de Toni-Fanconi syndrome. In this syndrome healing of rickets has not been observed with massive vitamin D therapy alone, as has frequently been tried in the past. Citrate has long been used in the treatment of lead poisoning, but its use has ordinarily been based upon the belief that it enhances the excretion of lead as a nontoxic lead-citrate complex.[11] Whether this is its principal action, however, remains in doubt,[12] and the suggestion has been made that citrate may promote storage of lead in bone.[13]

Summary of Long Bone X-Ray Changes

Period of Study	Date of X-Ray	Therapy	X-Ray Findings
I	1/27/53 (Fig. 3)	None (admission)	Osteoporosis with "ground glass" appearance of shafts of long bones; abnormally broad zones of epiphyseal cartilage; no gross deformities present; no bands of increased density, indicative of heavy metal deposition, present at ends of any bone, with possible exception of faint narrow lines (less than 1 mm.) at distal ends of radii
I	2/6/53	Edathamil calcium-disodium, 5 gm. (1/30-2/4/53)	No change
II	2/19/53	None	Osteoporosis unchanged; faint, irregular trabecular pattern replaces "ground glass" appearance in submetaphyseal areas; no calcification of rachitic cartilage; narrow but definite bands of increased density appear at metaphyses
III	3/7/53 (Fig. 4)	Citrate (2/25-3/13/53)	Some increase in mineralization with coarse irregular trabecular pattern in shafts and beginning healing of rickets in proliferative cartilage; no change in narrow bands of increased density noted on previous examination
IV	3/30/53 (Fig. 5)	None	Calcification of rachitic cartilage more marked; bands of increased density now quite dense, 2-3 mm. wide and present at ends of all long bones
V	5/11/53 (Fig. 6)	Citrate (3/30-8/3/53)	Continued excellent healing of rachitic process; bands of increased density widening
V	8/3/53	(3/30-8/3/53)	Rickets completely healed; bands of increased density and irregular calcified trabecular pattern receding from metaphyses and blending into shafts; new osteoid adjacent to metaphyses developing in uniform, orderly fashion; no gross deformities seen
VI	9/17/53 (Fig. 7)	None	Continued normal bone growth

Results.—Throughout the entire study several factors remained relatively constant and unaltered by therapy. Thus within a few days after the initial edathamil calcium-disodium therapy the blood lead concentration stabilized at 0.11 mg. lead/100 gm. whole blood. After eight months the concentration was 0.097 mg. lead/100 gm. whole blood. During the entire eight months of study, repeated analyses showed fecal lead outputs of 0.085 to 0.664 mg./24 hr., except for one value of 1.50 mg. lead/24 hr. obtained after hospitalization when there was other evidence of brief recurrent lead ingestion. With this possible exception, the values are within normal limits for lead in feces.[14] In the absence of diet analyses for lead, the variations are not necessarily significant. Serum sodium, serum potassium, and whole blood NPN determinations were always within normal limits, as were several fasting blood sugar determinations. Even in the presence of roentgenologic evidence of rickets, serum alkaline phosphatase activity remained within normal limits. Serum citrate levels fluctuated at random in the normal to slightly elevated range (patient, 2.2 to 4.0 mg. per 100 cc.; normal range, 1.8 to 3.3

mg.). (In ordinary vitamin-D-deficiency rickets the serum citrate concentration is reduced.[15]) On the 21st hospital day the endogenous creatinine clearance was 60 cc./min./1.73 sq. meter.

Other biochemical determinations did, however, reveal significant changes. To facilitate their presentation, the study of the patient may be divided into six periods with respect to therapy, as follows:

Period No.	Duration, Days	Therapy	Days of Observation
I	5	CaEDTA	4 to 8
II	21	Control	9 to 29
III	18	Citrate	30 to 47
IV	17	Control	48 to 64 *
V	132	Citrate	65 to 196
VI	45	Control	197 to 241

* Discharged from hospital on 66th day.

The urinary outputs of citrate, several aminoacids, glucose, and lead and the concentrations of serum calcium and phosphorus showed the most significant changes. These changes are plotted in Figure 1. Period I, relating to edathamil calcium-disodium therapy, is omitted from the graph. Results of serial roentgenologic studies of the long bones are summarized in the Table.

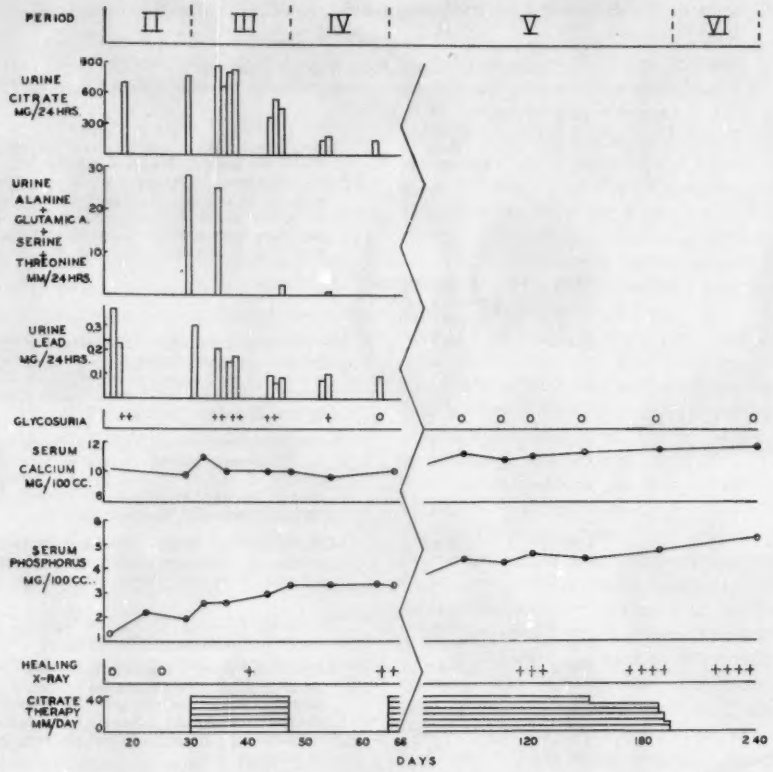


Fig. 1.—Changes in urinary outputs of citrate, several amino acids (alanine, glutamic acid, serine, and threonine) and lead, qualitative glycosuria, serum calcium and phosphorus, and the degree of roentgenologic healing of rickets are presented in relation to oral citrate therapy. The first portion of the graph shows the hospital studies; the latter portion, serum and x-ray studies obtained in the outpatient department.

Period II: Immediately following the edathamil calcium-disodium therapy a control period of three weeks was instituted. During the entire three weeks significant phosphaturia continued (daily urinary phosphorus outputs ranged between 240 and 334 mg./24 hr.), while the serum phosphorus concentrations remained low, fluctuating between 1.3 and 2.2 mg. per 100 cc. Serum calcium levels

were within the normal range. On two determinations urinary outputs of citrate were 688 and 750 mg./24 hr. Mild glycosuria continued in the presence of normal fasting blood sugar values. Urinary lead output was persistently elevated (0.227 to 0.374 mg./24 hr.).

Several qualitative chromatograms for urinary amino acids were obtained which indicated marked amino-aciduria. On the final 24-hour urine specimen of this period semiquantitative chromatographic determinations of those amino acids which appeared to be in the greatest excess were made, with the following results:

Amino Acid	Output, mM./24 Hr. Patient	Normal Range for Age [16]
Alanine	11.4	0 to 0.146
Glutamic Acid	1.95	0 to 0.231
Serine	11.5	0 to 0.162
Threonine	2.91	0 to 0.109

(In later urine collections the outputs of aminoacetic acid and tyrosine were also found to be significantly increased; however, quantitative estimations of these amino acids had not been made on any precitrate therapy urine specimen.) The changes in the sum of the urinary outputs of alanine, glutamic acid, serine, and threonine are presented in Figure 1. Outputs of all amino acids estimated quantitatively are presented in detail in Figure 2. Serum α-amino-acid nitrogen determinations were not obtained.

On admission a mild hyperchloremic acidosis was present, as indicated by serum chloride, 118.0 mEq. per liter; carbon-dioxide-combining power, 20.8 mEq. per liter. Despite adequate intake of food and water,

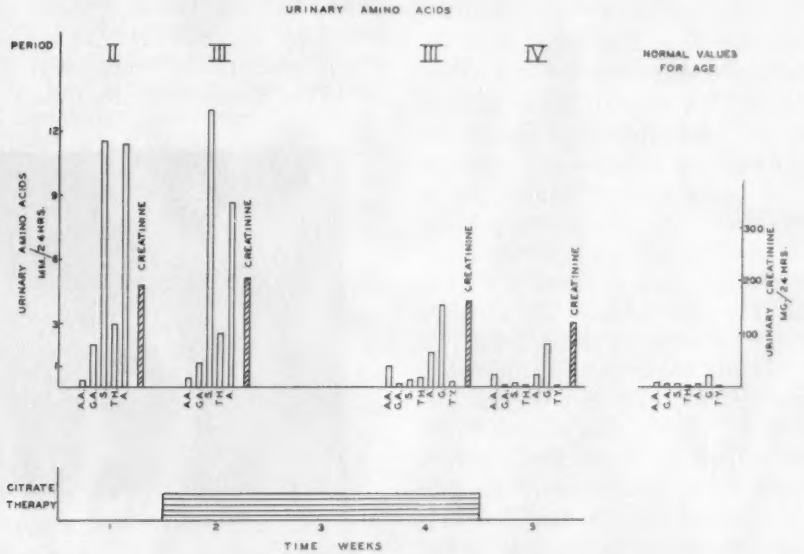


Fig. 2.—Quantitative urinary outputs of aspartic acid (A.A.), glutamic acid (G.A.), serine (S.), threonine (TH.), alanine (A.), aminoacetic acid (glycine) (G.), and tyrosine (TY.) before, during, and after citrate therapy (all values are ± 10 to 15%). These amino acids were in the greatest excess on qualitative chromatograms.

these values remained unchanged at the end of this control period. During this time the patient was secreting neutral to slightly alkaline urine.

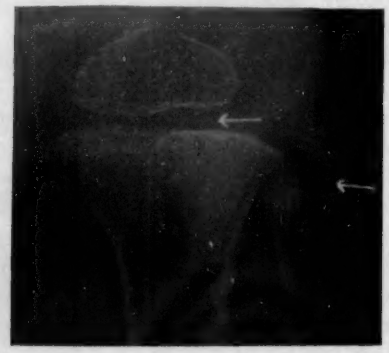
In summary, then, although a single course of edathamil calcium-disodium therapy effected a total urinary excretion of 21.2 mg. of lead, with a dramatic effect upon the patient's encephalopathy, three weeks later evidence of significant biochemical derangement persisted, namely, amino-aciduria, hypophosphatemia with phosphaturia, glycosuria, citraturia, skeletal changes of acute rickets with no roentgenologic evidence of signifi-

Figure 3.

cant deposition of lead in bone (Table 1), and mild hyperchloremic acidosis.

Period III: On the 30th day of observation the oral administration of sodium and potassium citrate was started, in a daily dose of 40 mM. citrate, 60 mM. sodium, and 60 mM. potassium. This was continued for 18 days. At the end of this time significant changes had occurred, as shown in Figures 1 and 2. The mild acidosis was corrected and did not later recur. Urinary amino acid output was still above normal, although it had decreased to about 25% of the pre-citrate-therapy value. Urinary citrate excretion was reduced by almost 50%. Urinary lead output fell to approximately one-third of the control levels. On the last three days of therapy the lowest fecal output of lead observed during the study was obtained (0.085 mg./24 hr.). Roentgenologically, on the 10th day of citrate therapy the earliest signs of healing of rickets appeared. Serum phosphorus concentration increased somewhat, from 1.9 to 3.3 mg. per 100 cc., while urinary phosphate excretion remained at the pretreatment level. The concentration of serum calcium showed no change.

Figure 4.



Period IV: Following the initial course of citrate therapy a second control period of 17 days was interposed. No vitamin D was given. During this time there was continued decrease of amino-aciduria and citraturia and the glycosuria disappeared. At the end of this period definite roentgenologic evidence of healing of rickets and of deposition of lead in bone became evident. Urinary lead output remained low. The serum phosphorus concentration remained at 3.3 mg. per 100 cc. Biochemically the patient's status was otherwise unchanged when compared with his status at the end of period III.

Figure 5.

Period V: Citrate therapy in the previous dosage was resumed, and on the 66th day of observation the patient was discharged home to continue the medication for a period of 132 days. Also, at home the child resumed consumption of evaporated milk in amounts providing 300 to 400 units of vitamin D daily. Quantitative 24-hour urine collections could not be obtained at home, but continued analyses of serum and roentgenologic studies of the long bones were obtained in the outpatient department. In the several partial urine collections obtained, concentrations of lead, citrate, and amino acids indicated no significant change from the status at the time of discharge. Fecal lead output and

blood lead concentration suggested some minor brief lead ingestion during the first month after discharge, although this was denied by the mother.

Serial long bone x-rays showed progressive excellent healing of the rachitic process, and at the time of cessation of citrate therapy normal ossification had replaced the previous abnormal picture. Coincident with the complete healing of rickets the serum phosphorus concentrations rose from borderline low levels (3.4 to 4.6 mg./100 cc.) to well within normal range (4.7 to 5.2 mg./100 cc.). During this time the serum calcium level rose somewhat, to 11.4 mg./100 cc. There was no residual hematologic or clinical evidence of active lead intoxication, but moderate mental retardation remained.

Period VI: Six weeks after the conclusion of citrate therapy no change had occurred. At a future date a brief hospitalization for study is planned.

COMMENT

The data presented pose a number of questions of both theoretical and clinical interest. The critical question, of course, is whether the rickets, hypophosphatemia, amino-aciduria, and glycosuria observed in the patient were the result of lead intoxication or of some coincidental metabolic defect or of preexisting vitamin D deficiency. This consideration points to the obvious parallelism between the findings in the patient and those seen in patients with the de Toni-Fanconi syndrome. Furthermore, what relationship, if any, is there between the patient's findings and those in ordinary vitamin D deficiency rickets. Of considerable clinical interest are the roles of the therapeutic agents (edathamil calcium-disodium and citrate) used in the case.

Figure 6.

Figure 7.

Available evidence, clinical, pathologic, and experimental, favors the conclusion that the biochemical disturbance was produced by lead and was neither coincidental nor the result of dietary vitamin D deficiency. The clinical and roentgenologic findings indicated that the rickets was of acute rather than of long-standing duration. It is true that the patient had received no vitamin D after 4 months of age except that in the evaporated milk, which provided daily intakes of 300 to 400 units of vitamin D; however, there were no deformities suggestive of old rickets.

Furthermore, although the urinary amino acid excretion pattern observed in the patient was strikingly similar to that recently reported in both dietary vitamin D deficiency and resistant rickets,[17] other biochemical differences were present. In the patient, serum alkaline phosphatase activity was never elevated. The patient's serum citrate levels were in the high normal to slightly elevated range, and urinary citrate excretion was not reduced, while in vitamin D deficiency plasma citrate levels and urinary excretion of citrate are usually low.[15] The rapid and complete recovery would argue against a congenital defect of the de Toni-Fanconi type.

Other clinical evidence indicates that lead can and has produced the various biochemi-

cal abnormalities observed in the patient. Review of Harriet Lane Home records disclosed several patients with lead poisoning in whom low serum phosphorus levels were found and some in whom rickets of varying degrees of severity was evident roentgenologically. The information available from these old hospital records was insufficient to be anything more than suggestive. In a child observed by us who died of acute lead encephalopathy, marked amino-aciduria was detected, and Wilson and co-workers [1] have also reported the occurrence of glycosuria and amino-aciduria in a child with lead poisoning. Finally, Caffey [2] described roentgenologic changes characteristic of hypoplastic rickets in a child with lead poisoning, which healed without supplementary vitamin D therapy. With healing, bands of increased density appeared at the ends of the long bones.

Both experimentally and clinically amino-aciduria and glycosuria have been described in saponated cresol solution, U. S. P. (Lysol) [18] and in uranium poisoning,[19] these substances being toxic to the renal tubule. In addition, threefold to fourfold increases in urinary citrate output have been observed in experimental uranium poisoning in rats.[20]

Pathologically, Follis and co-workers [21] commented upon the frequency of microscopic changes of rickets in the bones of children dying with lead intoxication. Blackman [22] has described in detail the microscopic findings in the kidney in childhood lead poisoning. The lesions were located in the loop of Henle and in the proximal convoluted tubule. He further noted the occurence of similar but less numerous lesions in some patients exposed to lead, who died prior to the onset of any clinical symptoms of lead poisoning. In chronic but not acute experiments he was able to produce such lesions in rats, rabbits, and guinea pigs. Thoelin and co-workers,[23] using histochemical techniques, recently noted in experimental lead poisoning in rats marked reduction of alkaline phosphatase activity in the proximal convoluted tubule, which is considered to be the site of glucose, amino acid, and phosphate reabsorption.[16]

The anatomic renal pathology in lead poisoning outlined above is indeed similar to the early and intermediate renal pathological findings in the de Toni-Fanconi syndrome.[24] Although, histologically, renal damage may be quite diffuse in this syndrome, the early anatomic changes tend to occur in the epithelium of the proximal convoluted tubule. In the few kidneys examined, the alkaline phosphatase reaction was negative.

The biochemical disturbance in our patient reveals a striking parallelism with that known to occur in the de Toni-Fanconi syndrome, in which rickets, hypophosphatemia, amino-aciduria, and glycosuria are prominent features. A final, but probably significant, point of similarity is revealed in the recent report by Bickel and Smellie [10] referred to previously, with respect to the efficacy of citrate therapy in this congenital metabolic defect. In our patient, following large doses of sodium and potassium citrate the same course of events was observed: the acidosis, glycosuria, and amino-aciduria disappeared, and the skeletal changes of rickets were well-healed after six months. Physiologically, therefore, it would appear that dysfunction of the same or related enzyme systems is involved: as a result of an inborn error of metabolism in the de Toni-Fanconi syndrome and due to the toxic action of lead in our patient. It is further suggested that an important site of this physiologic disturbance is the renal tubule.

There remains to be considered the influence upon the biochemical disturbance in the patient of the therapeutic agents used. With respect to edathamil calcium-disodium, it seems likely that this drug was not primarily responsible for the basic disturbance, although adequate serum and urine studies could not be obtained before it was administered. Roentgenologically, severe rickets was present prior to edathamil calcium-disodium therapy. When one considers, however, that edathamil calcium-disodium mobilizes and presents to the kidney for excretion far higher concentrations of lead than any pre-

vious "deleading" agent, the possibility cannot be ruled out that the lead-edathamil chelate is partially dissociated in the renal tubule, with the result that significant amounts of lead are thus freed in the tubule. In such a manner edathamil calcium-disodium might have intensified the injury to the renal tubule due to lead poisoning.

Review of Figures 1 and 2 and of other data presented shows that mild acidosis, amino-aciduria, glycosuria, hypophosphatemia, and rickets were still present three weeks after the completion of a single course of edathamil calcium-disodium therapy and that roentegenologically there was still no significant storage of lead in bone. After 16 days of citrate therapy amino-aciduria and glycosuria were greatly reduced and the earliest skeletal signs of the healing of rickets and of lead deposition had appeared. During the ensuing fortnight, however, when no therapy was given, continued improvement occurred. Thus, although there exists the possibility that the improvement observed was the result of progressive spontaneous recovery from lead poisoning, the rapidity of the improvement coincident with the institution of citrate therapy suggests quite strongly that citrate accelerated the rate of recovery. It will be recalled that in the case of Wilson and co-workers,[1] which was apparently less severe, amino-aciduria persisted for at least two months. A further characteristic of the healing of rickets under the influence of citrate is the fact that serum phosphorus concentrations remain low until, roentgenologically, healing is advanced. This phenomenon was observed in the patient.

Despite the fact that citrate has long been used in the therapy of clinical lead poisoning, the question of whether it promotes storage or excretion of lead remains in dispute. In the case presented, there was no roentgenologic evidence of significant lead deposition in bone prior to the institution of citrate therapy. Following citrate therapy there was no significant increase in the fecal excretion of lead, and the urinary output of lead decreased sharply, while significant "lead lines" appeared in the long bones coincident with the early signs of healing of the rachitic process. It would seem that the storage of lead in the skeleton rather than its excretion was enhanced during citrate therapy in this patient.

In summary, therefore, the data indicate that citrate accelerated the healing of rickets in the presence of a toxic concentration of lead which had produced the defect of calcification initially. As calcification of new bone occurred, lead was deposited with the new bone salts. With the removal of lead to a tissue where it was deposited in a physiologically inert form, the internal balance of lead metabolism was shifted and soft tissue concentrations of lead reduced. Coincident with this, evidence of biochemical renal tubular dysfunction disappeared. Whether citrate promoted the healing of rickets owing to a direct effect upon the calcification mechanism or through an effect upon renal tubular function, thus permitting the healing of rickets and deposition of lead, cannot be stated. The fact that the skeletal changes of rickets in the de Toni-Fanconi syndrome are usually resistant to large doses of vitamin D and that Bickel and Smellie [10] have observed good healing of rickets with the addition of citrate in this syndrome strongly suggests (in view of the similarity of the renal aspects of both this genetic defect and of lead poisoning), that citrate has an important effect upon renal tubular reabsorption mechanisms.

Further studies of the effects of lead poisoning upon renal tubular function are now in progress, as are further clinical studies to determine the significance and prevalence of such biochemical disturbances in childhood lead poisoning.

SUMMARY

A case of lead poisoning in a 33-month-old child is described. In addition to the usual well-known clinical findings of acute encephalopathy and anemia, this patient presented hypophosphatemia, glycosuria, amino-aciduria, and the skeletal changes of acute rickets. It is postulated that these findings were related and were primarily the result of a disturbance of renal tubular function due

to lead. This biochemical disturbance was reversible, for the abnormalities subsequently disappeared.

The similarity of this biochemical disturbance to that observed in the de Toni-Fanconi syndrome is pointed out. It is suggested that the same or related renal tubular enzyme systems are involved in lead intoxication.

It is suggested that, in this patient, the principal therapeutic effect of citrate was to accelerate the healing of rickets in the presence of lead-induced renal tubular dysfunction, with the simultaneous deposition and storage of lead in the newly-formed bone.

REFERENCES

1. Wilson, V. K.; Thomson, M. L., and Dent, C. E.: Amino-Aciduria in Lead Poisoning: A Case in Childhood, Lancet **2**:66, 1953.

2. Caffey, J.: Lead Poisoning Associated with Active Rickets: Report of a Case with Absence of Lead Lines in the Skeleton, Am. J. Dis. Child. **55**:798, 1938.

3. Kramer, B., and Tisdall, F. F.: A Simple Technique for the Determination of Calcium in Small Amounts of Serum, J. Biol. Chem. **47**:475, 1921.

4. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

5. Natelson, S.; Pincus, J. F., and Lugovoy, J. K.: Microestimation of Citric Acid: A New Colorimetric Reaction for Pentabromoacetone, J. Biol. Chem. **175**:745, 1948.

6. Hawk, P. B.; Oser, B. L., and Summerson, W. H.: Practical Physiological Chemistry, Ed. 12, Philadelphia, The Blakiston Company, 1947, p. 585.

7. McFarren, E. F., and Mills, J. A.: Quantitative Determination of Amino Acids on Filter Paper Chromatograms by Direct Photometry, Analyt. Chem. **24**:650, 1952.

8. Snyder, L. J.: Improved Dithizone Method for Determination of Lead: Mixed-Color Micromethod at High pH, Analyt. Chem. **19**:684, 1947.

9. Harrison, H. E., and Harrison, H. C.: Further Studies of the Effects of Citrate Feeding on the Calcium, Phosphorus, and Citrate Metabolism of Rachitic Infants, J. Pediat. **41**:756, 1952.

10. Bickel, H., and Smellie, J. M.: Cystine Storage Disease with Amino-Aciduria, Lancet **1**:1093, 1952.

11. Kety, S. S., and Letonoff, T. V.: Treatment of Lead Poisoning with Sodium Citrate, Proc. Soc. Exper. Biol. & Med. **46**:476, 1941.

12. Hardy, H. L.; Bishop, R. C., and Maloof, C. C.: Treatment of Lead Poisoning with Sodium Citrate, A. M. A. Arch. Indust. Hyg. **3**:267, 1951.

13. Smith, F. L.: Effect of Therapeutic Agents in the Treatment of Lead Poisoning, Safe Practice Bulletin No. 52, Department of Labor and Industry, Commonwealth of Pennsylvania, Harrisburg, Pa., 1941, p. 17.

14. Kehoe, R. A.; Thamann, F., and Cholak, J.: On the Normal Absorption and Excretion of Lead: II. Lead Absorption and Excretion in Modern American Life, J. Indust. Hyg. & Toxicol. **15**:273, 1933.

15. Harrison, H. E., and Harrison, H. C.: Vitamin D and Citrate Metabolism: Studies in Rachitic Infants, Yale J. Biol. & Med. **24**:273, 1952.

16. Eberlein, W. R.: Aminoaciduria in Childhood: Cystinuria and Cystinosis, Am. J. M. Sc. **225**:677, 1953.

17. Jonxis, J. H. P., and Huisman, T. H. J.: Amino-Aciduria in Rachitic Children, Lancet **2**:428, 1953.

18. Spencer, A. G., and Franglen, G. T.: Gross Amino-Aciduria Following a Lysol Burn, Lancet **1**:190, 1952.

19. Voegtlin, C., and Hodge, H. C.: Pharmacology and Toxicology of Uranium Compounds, New York, McGraw-Hill Book Company, Inc., 1949.

20. Haven, F. L., and Randall, C.: The Urinary Excretion of Citrate in Uranium-Poisoned Rats, J. Biol. Chem. **175**:737, 1948.

21. Follis, R. H., Jr.; Jackson, D.; Eliot, M. M., and Park, E. A.: Prevalence of Rickets in Children Between 2 and 14 Years of Age, Am. J. Dis. Child. **66**:1, 1943.

22. Blackman, S. S., Jr.: Intranuclear Inclusion Bodies in the Kidney and Liver Caused by Lead Poisoning, Bull. Johns Hopkins Hosp. **58**:384, 1936.

23. Thoelen, H.; Richterich, R.; Pletscher, A., and Staub, H.: Über das Verhalten von Aminosäuren und Fermenten bei Schwermetallvergiftungen: I. Die experimentelle, akute und subakute Bleivergiftung, Arch. exper. Path. u. Pharmakol. **215**:389, 1952.

24. Bickel, H., and others: Cystine Storage Disease with Aminoaciduria and Dwarfism (Lignac-Fanconi Disease), Acta pædiat. (Supp. 90) **42**:1, 1952.

THERAPY OF THE NEPHROTIC SYNDROME

Sodium Restriction, Dextran, and Corticotropin (ACTH) Alone or Combined with Nitrogen Mustard

LAWRENCE GREENMAN, M.D.
F. A. WEIGAND, M.D.
and
T. S. DANOWSKI, M.D., Pittsburgh

DURING the two and one-half years from April, 1951, to December, 1953, we have treated 30 children with the nephrotic syndrome at the Children's Hospital. Therapy has been divided into two phases: (1) the delivery of edema through rigid sodium restriction with or without the administration of dextran,* PVP (polyvinylpyrrolidone), or urea, and (2) an attempt to correct the renal abnormalities by administration of corticotropin (ACTH) alone or in combination with nitrogen mustard. All cases of nephrotic syndrome have been treated as they presented themselves, irrespective of whether or not they fell into the category of so-called "lipoid nephrosis." Diagnosis was based on currently accepted criteria.[1] The results indicate the beneficial effects of the above therapy but also illustrate a potential hazard.

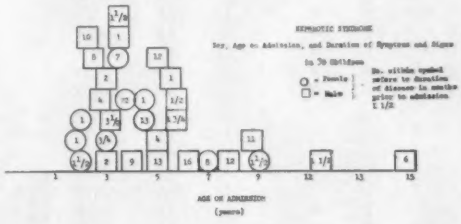
STATUS PRIOR TO TREATMENT

Physical Findings.—In the Figure, the sex, the age at admission, and the duration of the illness are shown. Generalized edema had been present in all prior to hospitalization but in only 28 at the time of entry into the hospital. Blood pressure readings were in general within the range of normal for the patient's age, though in one of the children persistent readings of 130/90 were obtained. The remainder of the examination was entirely negative save for the presence of a palpable liver in 10 patients.

Pre- and post-treatment data are presented in Tables 1 through 4.

The number of courses of therapy exceeded 30, since several of the children were re-treated. The data counted in the text of the paper reflect only the findings on the first admission of each person. The final follow-up results are dated from completion of the final course of corticotropin (Table 5).

Urinalysis (Table 1).—In serial examinations, profuse albuminuria was present in each instance; granular casts, red blood cells, or both were found in the spun sediments of early morning urine of all but two of the children. Benzidine tests were run to confirm the absence or presence of the erythrocytes. Quantitative urine proteins ranged as high as 15.9 gm. per liter in the six patients in whom such data were available. Insofar as could be determined from daily analyses, the specific gravity of the urine was not fixed in any of the patients.


NEPHROTIC SYNDROME
Sex, Age on Admission, and Duration of Symptoms and Signs
in 30 Children
O = Female
□ = Male
No. within symbol refers to duration of disease in months prior to admission.
AGE ON ADMISSION
(years)

The Figure indicates that the majority of the patients were less than 6 years old. There was no clear-cut history to suggest prior acute glomerulonephritis in any of them. Duration of illness ranged from 3 weeks to 22 months prior to admission; two-thirds of the patients were boys. Diagnosis was based upon history of insidious onset of edema, profuse proteinuria, and the other criteria described in the text.

Blood and Serum Solutes (Table 2).—The whole-blood nonprotein nitrogen was not elevated in 19 of the group, ranging between 27 and 39 mg. per 100 cc. It was 40 mg. per

Supported by grants-in-aid from the Medical Research and Development Board, National Drug Company, and Wyeth Laboratories, Inc.

From the Children's Hospital, the Renziehausen Foundation, and the Department of Research Medicine, University of Pittsburgh School of Medicine.

*Wyeth Laboratories, Inc., and the National Drug Company respectively, supplied the dextran (Plavolex) and corticotropin (ACTH) used in this study.

100 cc. in three, between 41 and 50 mg. in five, between 52 and 55 mg. in two, and 70 mg. in one other. The serum albumin levels were lower than 1.0 gm. per 100 cc. in 23 children and between 1.0 and 2.0 gm. in six ranged between 500 and 1,762 mg. per 100 cc. The readings in the other four on whom determinations were available were 444, 436, 425, and 327. The serum CO_2 content, chloride, sodium, potassium, and phosphorus

TABLE 1.—*Clinical Findings Prior to Corticotropin Treatment in Children with Nephrotic Syndrome*

Patient	Sex	Race	Age Yr.	Age Mo.	Duration of Disease Before Treatment Mo.	B.P., Mm. Hg	Edema*	Hepatomegaly*	Specific Gravity, Range	Albumin, Range*	R.B.C./H.P.F.	Granular Casts/H.P.F.
C. A.	F	W	2	11	0.8	94/54	4	0	1.033 to 1.042	4+ to 4+	0	1 to 4
B. B.	M	W	5	0	13.0	110/80	4	0	1.020	4+	12	0
L. C.	M	W	7	11	5.0	100/68	4	0	1.007 to 1.010	4+ to 4+	0	3 to 4
L. C.†	..	..	8	7	12.0	108/50	1	0	1.024 to 1.030	4+ to 4+	0 to 1	0
R. F.	M	W	2	9	3.5	110/62	4	+	1.025 to 1.035	4+ to 4+	7 to 8	0 to 0.1
D. F.	M	W	5	10	1.2	106/60	4	+	1.006 to 1.036	1+ to 4+	0	3 to 8
J. F.	M	W	2	2	2.0	100/64	4	+	1.030 to 1.042	4+ to 4+	0 to 2	0 to 1
R. G.	M	W	5	0	4.0	110/70	4	+	1.028	4+	30 to 40	4 to 8
S. G.	F	W	1	11	1.5	120/80	4	0	1.035 to 1.043	1+ to 4+	0	0
R. H.	M	W	3	9	0.5	108/68	4	0	1.013 to 1.042	1+ to 4+	0	0 to occ.
L. H.	F	N	9	0	1.7	104/66	4	0	1.012 to 1.020	4+ to 4+	0 to occ.	1 to 2
C. H.	F	W	4	6	13.0	110/70	4	+	1.018 to 1.034	4+ to 4+	0 to 2	2 to 20
W. J.	M	N	14	8	6.0	130/90	4	0	1.015 to 1.025	4+ to 4+	0	0 to 1
R. M.	M	N	5	6	1.0	100/40	4	+	1.017 to 1.036	1+ to 4+	0 to 15	0 to 3
K. M.	F	W	3	8	22.0	120/75	4	+	1.011 to 1.025	2+ to 4+	0 to 4	0 to 2
K. M.†	..	..	5	1	27.0	100/60	0	0	1.020 to 1.032	2+ to 3+	0	0
R. Min.	M	W	6	2	16.0	112/72	4	0	1.006 to 1.028	2+ to 4+	0 to 1	0 to many
E. N.	F	W	1	9	1.0	100/50	4	0	1.007 to 1.024	2+ to 3+	5 to 7	1 to 4
D. O.	F	W	7	0	8.0	110/80	4	0	1.028 to 1.034	4+ to 4+	6 to 20	1 to 3
E. P.	M	W	3	1	2.0	104/60	4	0	1.038	4+	0	1
A. P.	M	W	4	0	9.0	100/56	4	+	1.020 to 1.030	4+ to 4+	10 to 30	0
A. P.†	..	..	4	3	12.0	84/66	0	0	1.010 to 1.025	2+ to 3+	0	0 to 1
A. P.†	..	..	4	7	16.0	90/50	0	0	1.016 to 1.032	3+ to 4+	0	0
A. P.†	..	..	4	9	18.0	90/60	0	+	1.012 to 1.020	2+ to 4+	0	0 to 5
A. P.†	..	..	5	2	23.0	105/60	0	0	1.010 to 1.013	2+ to 3+	0	0
A. P.†	..	..	6	4	33.0	120/78	0	0	1.020	3+	0	4
M. P.	F	W	2	1	1.0	98/40	4	0	1.016 to 1.031	2+ to 4+	0 to 4	0
J. Ro.	M	W	2	6	8.0	90/60	4	0	1.024 to 1.027	4+ to 4+	5 to 50	5 to 10
J. Rob.	M	W	2	10	4.0	130/80	4	0	1.028	4+	0	0
J. Rob.†	..	..	3	5	11.0	110/60	4	0	1.007 to 1.035	1+ to 4+	0	0 to 4
R. R.‡	M	W	4	11	12.0	90/60	4	0	1.015 to 1.037	4+ to 4+	0 to 10	0 to 10
§	..	..	..	..	....	128/70	4	0	1.019 to 1.030	4+ to 4+	5 to 8	0 to 2
‖	..	..	..	..	....	140/70	4	0	1.007 to 1.025	2+ to 4+	0	0
E. R.	M	W	8	8	11.0	100/76	0	0	1.013 to 1.031	2+ to 4+	0 to 2	0 to 3
K. S.	F	W	4	5	1.0	90/60	4	0	1.034 to 1.044	4+ to 4+	2 to 5	0
R. S.	M	W	3	6	1.0	104/60	4	0	1.018 to 1.036	3+ to 4+	0	0 to 4
P. T.	F	W	3	6	7.0	105/70	4	+	1.008 to 1.028	tr. to 2+	0	0 to 4
S. T.	M	N	3	7	1.5	90/60	0	+	1.006 to 1.033	1+ to 4+	0	0 to 2
R. V.	M	W	11	7	1.5	96/70	4	0	1.002 to 1.022	1+ to 4+	0 to occ.	0 to 5
R. V.†	..	..	11	9	3.5	112/70	4	0	1.006 to 1.036	1+ to 4+	0 to 20	0 to many
M. W.	M	W	2	2	10.0	100/80	4	0	1.029 to 1.033	4+ to 4+	0	1 to 4

* Scale 1 to 4.
† Subsequent admission with a new course of corticotropin therapy.
‡ 12/15/52.
§ 12/27/52.
‖ 1/29/53.

others. One of the two patients without edema had a serum albumin of 3.5 gm. per 100 cc. The globulin values ranged between 1.7 and 4.1 gm. per 100 cc. All but a few of the patients had a distinct hypercholesteremia; in 25 the pretreatment cholesterol were usually not grossly abnormal, even in the patients with moderate elevations in nonprotein nitrogen. As might be expected in view of the changes in the serum proteins, the calcium concentration was usually reduced, ranging as low as 6.6 mg. per 100 cc.

All of these measurements were obtained by means of analytical techniques in regular use in this laboratory.[2]

size and shape, in addition to electrocardiograms, were obtained. In addition to the usual hospital routine recording of tempera-

TABLE 2.—*Blood and Serum Findings Prior to Corticotropin Treatment in Children with Nephrotic Syndrome*

	Blood		Serum										
Patient	N.P.N., Mg./ 100 Cc.	Sugar, Mg./ 100 Cc.	HCO_3, mEq./ L.	Cl, mEq./ L.	Na, mEq./ L.	K, mEq./ L.	TP, Gm./ 100 Cc.	Alb., Gm./ 100 Cc.	Glob., Gm./ 100 Cc.	Chol., Mg./ 100 Cc.	Ca, Mg./ 100 Cc.	P, Mg./ 100 Cc.	ASO Titer, Units/ Ml.
C. A.....	32	...	22.9	102.9	134	4.1	3.4	0.8	2.6	608	....	....	12
B. B.....	40	83	15.1	109.2	139	3.8	2.9	0.5	2.4	941	6.9	6.02	12
L. C.....	52	102	18.6	98.3	142	4.7	3.4	0.4	2.0	1,702	8.8	5.98	..
L. C.*.....	36	85	22.7	99.3	142	4.4	6.8	3.4	3.4	...	...	....	..
R. F.....	39	...	20.2	102.3	142	4.7	3.3	0.9	2.4	636	...	....	12
D. F.....	38	76	16.8	101.2	141	4.6	3.5	0.8	2.7	702	...	7.16	..
J. F.....	48	...	18.5	102.5	137	4.9	3.2	0.7	2.5	923	...	....	..
R. G.....	55	102	17.6	97.4	127	5.2	3.9	0.4	3.5	1,200	...	....	12
S. G.....	32	66	....	98.7	140	5.4	3.2	1.1	2.1	516	8.7	5.60	12
R. H.....	27	71	21.4	102.5	139	4.7	4.1	1.7	2.4	632	8.3	4.07	..
L. H.....	70	100	19.8	96.2	138	4.9	5.1	2.0	3.1	545	...	....	12
C. H.....	40	82	20.8	95.9	135	6.0	3.8	0.3	3.5	800	8.0	5.07	..
W. J.....	36	89	26.6	102.3	143	5.2	4.8	1.7	3.1	600	9.2	5.17	..
R. M.....	36	85	22.7	104.6	142	4.7	4.4	1.2	3.2	1,021	...	....	..
K. M.....	46	113	20.4	106.5	140	5.4	3.3	0.1	3.2	762	6.6	5.20	..
K. M.*.....	33	80	20.2	107.1	142	4.5	5.6	4.0	1.6	397	10.4	4.81	..
R. Min.....	36	80	24.8	105.1	139	5.4	4.1	0.5	3.6	827	...	....	..
E. N.....	35	77	18.4	98.8	142	4.9	3.3	0.3	3.0	...	8.0	4.89	12
D. O.....	31	...	23.3	107.3	141	5.0	3.3	0.6	2.7	436	8.2	5.22	..
E. P.....	35	74	16.9	104.5	140	4.8	4.5	0.4	4.1	444	9.1	5.47	12
A. P.....	28	62	22.2	98.2	141	4.3	3.4	0.4	2.5	1,021	...	....	..
A. P.*.....	26	...	24.7	102.8	151	5.6	5.5	3.3	2.2	242	...	....	..
A. P.*.....	31	...	....	102.4	140	4.6	5.7	3.2	2.5	259	...	....	..
A. P.*.....	28	78	24.7	99.9	143	...	5.4	3.6	1.9	267	...	....	..
A. P.†.....	28	...	22.5	103.9	146	4.5	4.5	1.8	2.7	343	8.6	5.98	..
A. P.*.....	34	91	22.0	101.5	144	4.0	5.7	2.6	3.1	358	9.0	4.91	..
M. P.....	30	77	16.2	104.1	133	4.9	3.8	0.9	2.9	606	9.1	6.02	..
J. Ro.....	43	...	21.2	103.3	138	3.6	1.9	0.2	1.7	676	...	....	..
J. Rob.....	27	100	20.2	101.8	132	4.9	3.3	1.4	1.9	750	9.2	....	..
J. Rob.*...	31	95	22.1	98.7	140	5.7	3.4	0.5	2.9	516	8.8	5.43	..
R. R.‡.....	45	104	12.5	104.1	137	5.4	3.3	0.2	3.1	1,412	7.8	6.80	..
§.....	24	...	20.0	109.3	130	5.0	...	...	...	...	...	....	..
‖.....	30	103	15.5	98.8	132	5.0	2.6	0.5	2.1	...	...	....	..
E. R.....	35	79	23.1	101.1	142	4.6	5.9	3.5	2.4	327	9.9	4.63	..
K. S.....	40	72	....	.....	...	...	3.5	0.7	2.8	545	...	....	..
R. S.....	33	...	17.9	105.6	138	5.0	3.8¶	0.7¶	3.1¶	533	...	....	12
P. T.....	34	...	....	.....	...	...	3.6	0.6	3.0	787	...	....	12
S. T.....	26	...	18.6	104.3	...	...	3.7	0.6	3.1	1,371	...	....	..
R. V.....	50	87	23.2	95.6	130	6.4	3.7	0.7	2.0	545	...	....	..
R. V.*.....	44	60	14.3	94.1	130	4.5	2.7	0.2	2.5	873¶	7.5	8.61	..
M. W.....	32	79	18.8	104.1	140	4.8	3.3	0.3	3.0	425¶	8.4	5.77	..

* Subsequent admission with a new course of corticotropin.
† Subsequent admission with a new course of corticotropin; had been on oral cortisone regimen, 50 mg./day, for 108 days.
‡ 12/15/52.
§ 12/27/52.
‖ 1/29/53.
¶ Within one week of other blood analyses.

STUDY AND TREATMENT REGIMEN

Laboratory and Other Procedures.—On admission, tuberculin skin tests, serological tests for syphilis, and, in one-third of the patients, antistreptolysin O titers were determined. Erect teleroentenograms for heart

ture and pulse rate at regular intervals, morning blood pressure readings were taken by nurses, with frequent checking by the physician. Daily body weight and the admission and the discharge height were recorded. At weekly intervals and at times more frequently the following were obtained: nose

and throat cultures; complete blood cell count, including eosinophiles; Wintrobe sedimentation rate; analyses of blood for non-protein nitrogen and sugar, and analyses of serum for total carbon dioxide content, chloride, sodium, potassium, total protein, albumin, globulin, and cholesterol levels. Daily morning specimens of urine were analyzed for specific gravity, acidity, albumin, sugar, and microscopic findings. At intervals urine was collected for 24 hours and analyzed for protein and sodium. Before discharge, the kidneys and ureters were visualized by intravenous pyelography.

TABLE 3.—*Clinical Findings at End of Corticotropin Treatment in Children with Nephrotic Syndrome*

	Therapy				Edema at Onset Corticotropin Treatment	Blood Pressure, Mm. Hg	Urine			
Patient	HN_2, Mg./Kg.	Cortisone, Mg.	Corticotropin, Mg.	Treatment, Days			Sp. Gr.	Alb.	R.B.C./H.P.F.	Granular Casts/H.P.F.
C. A.	0.3	.....	2,800	28	0	118/88	1.014	0	0	0
B. B.	0.3	.....	2,800	28	4 *	118/80	1.018	3+	0.5	0.5
L. C.	...	3,990	0	12	0	120/84	1.007	1+	0	0
†	0.3	.....	1,000	10	0	112/52	1.035	2+	0	0
L. C.‡	0.6	.....	5,600 *	56	0	155/125	1.011	1+	0	0
R. F.	0.3	.....	2,800	28	0	120/64	1.016	2+	0	0.5
D. F.	0.3	.....	2,800	28	0	104/78	1.014	0	0	0
J. F.	0	.....	2,800	28	0	100/76	1.020	0	0	0
R. G.	0.3	.....	2,800	28	4 *	130/70	1.014	1+	2	1
S. G.	0.3	.....	2,500	25	4 *	100/66	1.013	Trace	0	0
R. H.	0.3 §	.....	2,800	28	0	98/54	1.030	3+	0	0
L. H.	0.3	.....	2,800	28	4 *	100/84	1.013	1+	0	0
C. H.	0.3	.....	3,800	29	4 *	108/58	1.023	2+	0	0
W. J.	0.3	.....	2,800	28	0	100/60	1.006	1+	0	0
R. M.	0.3	.....	2,800 ‖	28	0	110/50	1.011	0	0	0
K. M.	0	1,600	0	16	4 *	98/68	1.015	1+	0	0
	0	0	200	5						
K. M.‡	0.3	.....	3,000	30	0	106/88	1.028	2+	0	0
R. Min.	0.3	.....	3,000	30	0	100/64	1.013	1+	0	0
E. N.	0	.....	2,800	28	0	110/76	1.024	0	0	0
D. O.	0.3	.....	2,800	28	0	126/70	1.023	Trace	0	0
E. P.	0.3	.....	2,800	28	0	100/70	1.014	0	0	0
A. P.	0.3	.....	2,700	30	0	116/60	1.021	0	0	0
A. P.‡	0.3	.....	3,100	31	0	120/78	1.018	0	0	0
A. P.‡	0	.....	1,900	19	0	80/60	1.023	0	0	0
A. P.‡	0	.....	2,800	28	0	114/74	1.020	0	0	0
A. P.‡	0.2	.....	2,440	26	0	98/60	1.024	0	0	0
A. P.‡	0	.....	2,800	28	0	110/74	1.013	0	0	0
M. P.	0	.....	3,800 ‖	38	4 *	122/80	1.010	0	0	0
J. Ro.	0.3	.....	2,800	28	0	120/78	1.010	1+	0	0
J. Rob.	0	.....	2,800	28	0	110/70	1.029	0	0	0
J. Rob.‡	0.3	.....	2,800	28	4 *	120/64	1.012	0	0	0
R. R.¶	0.3	.....	300	3	4 *	130/90	1.030	4+	0	0
‡‡	0	.....	1,000	10	4 *	164/124	1.021	4+	0	0
**	0	.....	300	3	4 *	150/120	1.019	2+	0	2
E. R.	0.3	.....	2,100 ††	21	0	120/88	1.026	4+	0	0
K. S.	0	.....	2,800	28	4 *	116/70	1.040	Trace	0	0
R. S.	0.3	.....	2,800	28	4 *	130/62	1.017	0	0	0
P. T.	0	.....	2,800	28	4 *	120/90	1.024	0	0	0
S. T.	0.3	.....	2,800	28	4 *	110/50	1.030	4+	0	0
R. V.	0	.....	1,850	20 ‡‡	4 *	110/64	1.015	1+	0	0
R. V.‡	0.3	.....	3,800	38	4 *	118/84	1.007	1+	0	0
M. W.	0.3	.....	2,800	28	0	124/76	1.013	0	0	0

* ACTX—National Drug Company form of corticotropin; received 0.25 cc. q. 6 hr. IM for 28 days then 0.50 cc. q. 6 hr. for an additional 28 days.
† Same admission but findings at end of cortisone therapy.
‡ End of subsequent course of corticotropin.
§ Given at end of corticotropin therapy.
‖ Corticotropin, 0.50 cc. q. 6 hr.
¶ 12/18/52.
‡‡ 1/6/53.
** 2/1/53.
†† Corticotropin, 0.25 cc. q. 6 hr.
‡‡ For preceding 9 days received IV corticotropin, 25 mg. in 500 cc. 5% dextrose water each day.

Diet.—The patients were given a calorically adequate diet which provided 2 to 9 mEq. of sodium, about 150 mEq. of potassium, and 3 gm. of protein per kilogram of body weight each day. Supplementary iron and vitamins were given.

Antibiotics.—An antibiotic, usually penicillin, was given prophylactically even though β hemolytic streptococci were isolated from only one of the children and antistreptolysin O titers remained low (12 units) in the 10 children in whom they were measured. The

TABLE 4.—*Blood and Serum Findings at End of Corticotropin Treatment in Children with Nephrotic Syndrome*

	Blood		Serum									
Patient	N.P.N., Mg./100 Cc.	Sugar, Mg./100 Cc.	HCO_3, mEq./L.	Cl, mEq./L.	Na, mEq./L.	K, mEq./L.	TP, Gm./100 Cc.	Alb., Gm./100 Cc.	Glob., Gm./100 Cc.	Chol., Mg./100 Cc.	Ca, Mg./100 Cc.	P, Mg./100 Cc.
C. A.	36	96	23.3	101.7	146	4.7	5.5	3.2	2.3	249	9.7*	3.80*
B. B.	32	106	21.7	102.5	138	3.2	3.0	0.8	2.2	361	7.7*	3.80*
L. C.†	25	91	22.8	89.3	120	4.4	2.1	0.6	1.6	...	9.0*	3.62
‡	35	68	25.3	103.3	144	5.1	5.9	3.4	2.6	...	....	....
L. C.§	22	117	31.3	66.1	112	2.3	4.8	3.1	1.7	...	8.0	2.50
R. F.	27	...	24.6	98.9	145	4.6	5.4	3.2	2.2	329	....	....
D. F.	31	83	26.8	92.5	141	3.7	5.2	3.1	2.1	205	....	....
J. F.	25	...	20.8	100.2	138	4.7	5.7	3.6	2.1	270	....	....
R. G.	37	80	23.0	103.0	137	3.9	5.0	2.2	2.8	407	....	....
S. G.	26	76	....	98.7	140	5.4	5.6	3.3	2.3	298	....	....
R. H.	34	62	26.1	97.5	144	4.2	5.4	3.3	2.1	291	9.7	4.23
L. H.‖	28	...	21.7	98.7	145	4.6	7.1	4.5	2.6	203	....	5.77
C. H.	43	174	22.0	99.0	143	4.2	4.6	2.4	2.2	361	9.7	3.07
W. J.	25	86	26.9	93.0	145*	4.6*	6.1	3.5	2.6	402	10.7*	4.33*
R. M.	30	111	26.4	91.2	142	4.5	5.6	3.6	2.0	417	9.7	4.15
K. M.	32	...	20.6	107.3	...	...	5.6	2.7	2.9	188	....	....
K. M.¶	39	96	24.2	93.9	142	4.9	6.6	4.4	2.2	372	9.9*	5.40*
R. Min.	34	94	25.0	97.7	146	5.3	6.2	...	...	...	....	4.02
E. N.	25	100	20.1	103.3	148	4.8	6.4	3.6	2.8	294	10.2	5.22
D. O.	31	104	27.1	96.1	144	4.5	6.0	3.2	2.8	387	10.0	4.37
E. P.	31	...	23.9	98.4	141	4.8	5.5	3.1	2.4	274	9.4	5.13
A. P.	34	82	24.1	98.8	138	5.3	6.9	3.8	3.1	312*	11.0	5.83
A. P.¶	40	71	27.4	101.7	144	4.4	6.4	3.4	3.0	...	....	....
A. P.¶	34	...	27.4	101.2	144	5.0	5.8	3.8	2.0	231	....	....
A. P.¶	35	93	27.2	100.0	144	...	5.8	3.7	2.1	207	....	....
A. P.¶	27	...	25.6	.....	141	4.1	5.6	3.5	2.1	175	....	....
A. P.¶	33	96	25.7	94.3	146	4.2	6.9	4.5	2.4	375	11.1	6.13
M. P.	24	102	24.8	99.4	138	5.5	5.6	3.5	2.1	279	10.9	5.20
J. Ro.	33	75	23.9	100.5	...	...	5.6	1.8	3.8	494	8.8	4.73
J. Rob.	32	106	18.2	101.2	142	4.6	6.6	3.9	2.7	192	10.5	4.58
J. Rob.¶	37	81	22.4	100.6	143	4.9	6.2	3.8	2.4	318	10.5*	4.60
R. R.#	43	...	15.7	84.0	114	7.6	1.6	0.8	0.8	...	....	....
**	33	176	16.2	88.6	116	5.9	2.8	1.1	1.7	...	8.3	5.93
††	56	123	7.5	101.8	125	5.2	2.4	0.8	1.6	132	6.5	3.97
E. R.‡‡	42	74	23.8	98.4	136	5.0	5.5	3.3	2.2	250	....	....
K. S.	37	115	20.8	99.6	142	4.0	5.2	3.3	1.9	314	....	....
R. S.	30	102	23.1	94.5	142	4.2	5.9	3.1	2.8	457	....	....
P. T.	33	87	26.2	94.6	144	4.3	6.8	4.1	2.6	300	10.2	4.37
S. T.	29	121	18.0	98.9	134	5.7	6.9	4.0	2.9	457	....	....
R. V.	23	...	24.7	102.3	138	4.6	4.0	0.5	3.5	304	....	....
R. V.¶	37	83	28.2	98.9	142	4.4	4.8	2.5	2.3	356	9.9	3.62
M. W.	30	113	24.7	98.1	145	5.0	4.6	2.7	1.9	...	8.3	4.21

* This measurement was not obtained simultaneously with others in series but usually in a week or less.
† Treatment interrupted for 2 days. Patient developed serum Na of 120 mEq./L., hypertension, and headache.
‡ Cortisone treatment, 300 mg. q. d. for 13 days.
§ Findings at end of subsequent course of corticotropin; at end of interval following an IV injection of HN_3, patient developed headache and convulsions with indicated changes.
‖ 17 days after treatment completed.
¶ Findings at end of subsequent course of corticotropin.
# 12/18/52, treatment discontinued; patient received sodium-free dextran with increase in serum Na to 132 mEq./L. with diuresis.
** 1/6/53, associated with convulsion and hypertension.
†† 2/1/53, associated with convulsion and hypertension.
‡‡ Depression.

oral dosage was 100,000 units three times a day; in the case of the intramuscular route, 400,000 units was given each day. A few patients received either oxytetracycline (Terramycin) or chlortetracycline (Aureomycin); one child in whom peritonitis developed was treated with streptomycin for a short interval.

Diuretics.—Two patients received urea prior to corticotropin therapy. Eighteen patients were given colloid, 6, 12, or 20% dextran, or 3.5% polyvinylpyrrolidone (PVP), with or without sodium. Usually 500 ml. was infused each day during a four- to six-hour interval for a total volume ranging up to 7,200 ml. The blood pressure and the pulse and respiratory rates were recorded at 15-minute intervals prior to and during the administration of the fluid. Rectal temperature readings were obtained at half-hour intervals. The body weight, the urine output, the relative blood cell volume, the hemoglobin level, and the concentrations of blood and serum solutes were determined before and immediately after the infusion, as well as 3 and 24 hours later.

Corticotropin Therapy.—Corticotropin (National Drug Company or The Armour Laboratories) was given intramuscularly in a dosage of 25 mg. every six hours for 28 days. The last five patients received corticotropin alone; the other 25 were also given nitrogen mustard, 0.3 mg. per kilogram body weight, usually on the third day of corticotropin therapy.

All patients were kept at bed rest.

TABLE 5.—*Clinical, Urine, Blood, and Serum Analyses When Last Examined*

Patient	Mo. After Last Treatment	B.P., Mm. Hg	Urine		R.B.C./ H.P.F.	Granular Casts/ H.P.F.	Blood N.P.N., Mg./ 100 Cc.	Serum			
			Sp. Gr.	Albumin				TP, Gm./ 100 Cc.	Alb., Gm./ 100 Cc.	Glob., Gm./ 100 Cc.	Chol., Mg./ 100 Cc.
C. A.	6.5	92/50	1.029	Trace	0	0	30	6.3	3.9	2.4	361
B. B.	7.0	105/70	1.038	4+	0	0	37	5.8	3.6	2.2	296
L. C.	13.0	110/70	1.028	0	0	0	31	6.4	4.0	2.4	197
R. F.	7.0	100/45	1.025	1+	0	0	32	6.7	4.0	2.7	198
D. F.	8.0	105/80	1.023	0	0	0	35	7.4	4.8	2.6	141
J. F.	12.0	80/50	1.027	0	0	0	35	6.0	4.0	2.0	249
R. G.*	2.0	100/60	1.028	2+	0	0	30	5.9	3.6	2.3	294
S. G.	9.0	110/60	1.032	Trace	0	0	29†	6.8†	4.4†	2.4†	215†
R. H.	20.0	105/60	1.033	0	0	0	39	6.6	4.4	2.2	249
L. H.	9.0	126/58	1.025	0	0	0	21	6.8	4.0	2.7	291
C. H.	9.0‡	.....	.....	..	..	..	..	...	...	...	...
W. J.	1.0	120/80	1.015	4+	1	0	31	4.5	2.1	2.4	533
R. M.	9.0	90/50	1.032	0	0	0	32†	6.3	3.4	2.9	...
K. M.	22.0	100/58	1.032	1+	0	0	34	7.1	4.7	2.5	172
A. Min.	24.0	.....	1.011	0	0	0	..	...	...	...	...
E. N.	3.0	96/60	1.027	Trace	0	0	39	6.9	4.5	2.4	258
D. O.	6.0	100/55	1.025	0	0	0	36	7.2	4.4	2.8	286
E. P.	7.0	110/80	1.023	0	0	0	36	6.8	4.7	2.1	194
A. P.	1.0	110/70	1.014	0	0	0	32†	7.6†	4.8†	2.8†	375†
M. P.	16.0	84/60	1.010	0	0	0	32	6.0	3.6	2.4	294
J. Ro.	24.0	110/80	1.024	1+	0	0	..	...	...	...	...
J. Rob.	3.0	132/54	1.034	0	0	0	32	7.2	4.3	2.9	267
R. R.	7.0	120/80	1.016	3+	6	1	44	4.5	1.0	3.4	623
E. R.	2.0	110/80	1.030	3+	0	occ.	27†	6.1†	3.9†	2.2†	333†
K. S.	4.0	100/50	1.026	Trace	0	0	32	6.9	4.5	2.4	222
R. S.	1.5	108/60	1.022	0	0	0	30	6.3	4.0	2.3	...
P. T.	1.0	100/60	1.027	0	0	0	29†	7.0	4.8	2.2	242
S. T.	18.0	108/50	1.030	0	0	0	30†	7.3†	4.3†	3.0†	331†
R. V.	21.0	110/60	1.028	0	0	0	33	8.2	4.5	3.7	268
M. W.	1.0	124/64	1.020	0	0	0	27	5.8	3.5	2.3	261

* Letter from mother at 4 months indicates youngster is well.
† Nearest blood and serum analyses within 2 months of urinalysis.
‡ Letter from Brazil indicates normal findings.

RESULTS

Delivery of Edema Prior to Corticotropin Therapy.—Of the 28 patients with generalized edema present on admission, 16 received dextran or PVP, and diuresis ensued in 12.

This was frequently preceded by a disappearance of facial and peripheral edema. Dextran was also given to the two nonedematous patients without change in the body weight. In 10 children with edema unresponsive to or not treated with colloid, rigid sodium restriction, 2 to 9 mEq. per day for one and one-fourth to four months, was followed by diuresis in 3, with loss of edema in 11 to 16 days. In one of these, urea was also administered. Paracentesis abdominalis was performed in four patients. No attempt to deliver edema prior to corticotropin therapy was made in two others.

Effects of Corticotropin with and Without Nitrogen Mustard on Edema, Urinary Abnormalities, and Blood and Serum Solutes.—Almost all of the 25 patients receiving nitrogen mustard in conjunction with corticotropin developed nausea and vomiting during and for a period of hours after the administration of nitrogen mustard. None developed bone marrow depression or leucopenia.

One patient in whom diuresis had occurred on dextran therapy, reaccumulated edema fluid in the two-week interval that elapsed prior to corticotropin therapy. There were, therefore, 14 with edema when the hormone was started. Of the 14 patients, 11 had diuresis following one to two weeks of hormone therapy; another lost the excess fluid gradually, becoming nonedematous at the end of four weeks; two others had a diuresis after corticotropin was discontinued. Three, including the last two, required paracenteses during treatment.

At the completion of the initial course of treatment, 12 patients had completely normal urinalyses (Table 3). In 11 others, only trace or 1+ albuminuria was present, with granular casts and microscopic hematuria in one (R. G.). The remaining seven still had 2+ to 4+ albuminuria. In this last group, five had normal microscopic sediments, while two continued to have granular casts. One of the two had microscopic hematuria.

At the time corticotropin administration was discontinued the nonprotein nitrogen values were less than 38 mg. per 100 cc. in all but three children (Table 4). The serum albumin had risen to 4.0 to 4.5 gm. per 100 cc. in 3 patients, to 3.5 to 4.0 gm. in 5, to 3.0 to 3.5 gm. in 13, to 2.0 to 3.0 gm. in 4, and to only the 1.0 to 2.0 gm. range in one other. In three children, this value was still less than 1.0 gm. per 100 cc. No data are available in the remaining patient. The globulin concentrations ranged between 1.6 and 3.5 gm. per 100 cc., indicating values not greatly different from the pretreatment ones. The cholesterol in serum decreased toward or to normal: the level was less than 301 mg. per 100 cc. in 14 of the 27 patients in whom measurements are available, 301 to 350 mg. in another four, 351 to 400 mg. in three, and between 401 and 500 mg. in six.

Since an equally good response was obtained with corticotropin alone, we have no evidence from our data that any additional benefit was derived from the inclusion of nitrogen mustard in the treatment regimen.

Complications During Therapy.—Despite the rigid sodium restriction, only 3 patients of the entire group of 30 developed serum sodium concentrations below 132 mEq. per liter. One had been edema-free prior to administration of corticotropin; the other two were definitely edematous. The serum sodium fell to 124 mEq. per liter in the first edematous child after two days of corticotropin. He had had a paracentesis four days beforehand and was reaccumulating edema and ascites despite a diet containing 2.5 mEq. of sodium per day. The corticotropin was discontinued; infusion of 500 ml. of 6% dextran in isotonic saline was followed by a diuresis and increase in serum sodium to 132 mEq. per liter. Ten days later treatment with corticotropin was resumed, plus sodium restriction. He had no subsequent decrease in serum sodium and gradually lost his edema.

The other two patients with hyponatremia developed convulsions. One (L. C.) had been treated with corticotropin several months earlier, with the occurrence of a serum sodium of 120 mEq. per liter after eight days of corticotropin. In addition he had a severe headache with definite hypertension, and so therapy was discontinued. He was readmitted

because of persistent urinary and biochemical abnormalities. During the second course of corticotropin, he gained approximately 1 kg. of body weight per week despite a diet rigidly limited in sodium. Edema had not been present on admission. After an injection of nitrogen mustard on the 56th day, he developed severe convulsions, which produced anoxia and ultimately cerebral atrophy. His serum sodium had decreased to 112 mEq. per liter, with hypochloremia, alkalosis, and a low serum potassium concentration. Five days earlier his serum electrolytes had been normal and his urine contained less than 5 mEq. of sodium per day. He had marked hypertension during this interval. Thirteen months later he had no evidence of kidney disease.

The third patient (R. R.) had been ill for more than a year and had no diuresis with colloid. In the hospital he developed diarrhea but gained weight, even though his diet was rigidly limited in sodium. After nine days of corticotropin, the serum sodium was 116 mEq. per liter and the blood pressure was greatly increased. The urine contained 4 mEq. of sodium per liter during this period. He had a severe convulsion, which stopped after treatment with phenobarbital, desoxycorticosterone acetate, and hypertonic saline. Corticotropin was resumed at the end of three weeks. In three days he had another convulsion, with hypertension and a serum sodium level reduced to 125 mEq. per liter. He has had no further corticotropin and is apparently developing chronic glomerulonephritis.

The rest of the patients maintained normal serum sodium levels despite the rigid restriction. As a matter of fact, a number of children with sodium concentrations at the lower limit of normal prior to corticotropin therapy developed higher levels as treatment and the very low sodium intake continued.

Other complications of therapy included mental depression in one patient, necessitating cessation of treatment after two weeks. This patient now is well after retreatment. Peritonitis developed in one child after one day of corticortopin. It was treated successfully with streptomycin and penicillin after cessation of corticotropin. Subsequently, corticotropin was started again without difficulty, and the patient responded well. Upper respiratory infections were the commonest problem, but they subsided under routine management. A number of patients had minor elevations in blood pressure. In the two with convulsions, however, the increases were extreme, reaching 130/118 and 180/128. One patient developed temporary carbohydrate intolerance manifested by glycosuria and a diabetic type glucose tolerance test. This did not necessitate insulin and disappeared shortly after therapy was discontinued. All the children developed moon facies, protuberant abdomens, and cervical fat pads. Only three patients developed striae; these faded subsequently but did not disappear. Acne appeared in the older children, and in a number of patients hirsutism was temporarily evident.

Follow-up Data (*Table 5*).—The patients were followed in the outpatient department at first at two-week and one-month intervals and then every three months. Total duration of follow-up now extends from 1 to 24 months. During this time, there have been a total of six recurrences in two patients who had remained well for intervals of three to seven months. One treated for an exacerbation with edema at the end of seven months seems to be well again with a follow-up of only three months. The other patient has now undergone his sixth course of therapy with complete clearing of abnormalities one month after his last course. At one time he received cortisone to prevent relapse, but the amount, 50 mg. a day, proved inadequate. Patient A. P. was treated six times with corticotropin for recurrences of his nephrotic syndrome. He provides one of our strongest indications that corticotropin induces remissions in this illness. The remissions were temporary, however. Intervals between his courses of therapy varied from 2 to 10 months (Table 1). The recurrences usually began with increasing proteinuria and were followed shortly by a decrease in serum albumin concentration and an increase in cholesterol (Table 2). The first three retreat-

ments were carried out within a month of recurrence; however, the last two were withheld for five and seven months, respectively, after abnormalities appeared to see whether he would recover spontaneously. When he did not he was treated. Again, within two weeks his urine became protein-free, and by the end of a month there was a reversal of his abnormal biochemical changes (Table 4). The rapidity and consistency with which remission occurred with treatment after waiting prolonged intervals without spontaneous improvement in his condition was impressive. Three children (L. C., K. M., R. V.) in the original group of eight with the least improvement were re-treated several months and one year after the first course. L. C. and R. V. were edematous. Two ended their second course with 1+ albuminuria, and one had 2+ albuminuria. All had normal urinary microscopic examinations; two had slightly elevated serum cholesterol concentrations. In one patient, the serum albumin was normal.

At the last examination of this group of patients, 22 (73%) of the 30 had normal urinalyses (4 of them had traces of albumin in their urine); 1 of the patients with a trace of albumin had a slightly elevated serum cholesterol concentration. The other 21 had normal biochemical findings as recorded (Table 5). Four other patients have 1+ to 2+ proteinuria, with normal biochemical findings. A letter from the mother of one of these children (R. G.) four months after treatment suggests that his physician found the urine normal. There are only four (13%) children who are definitely abnormal: two have hypertension, three have abnormal urines, two have low serum proteins, and three have abnormally increased cholesterol findings; the nonprotein nitrogen is elevated in one. One patient, B. B., still has a nephrotic syndrome but is nonedematous and has shown some improvement in biochemical abnormalities. Only R. R. still had minimal edema when being followed in clinic.

COMMENT

There is no question in view of the data presented that the treatment program employed in these 30 patients induces remissions of the nephrotic syndrome. At this point it is reasonable to suggest that nitrogen mustard when used in the manner described in the present report is not a necessary adjunct. This is in keeping with the current status of nitrogen mustard as the sole treatment of renal diseases.† It is not possible, however, to ascribe the beneficial results entirely to the adrenocorticotropic hormone. This is particularly so when it is recalled that the clinical results of others employing corticotropin or cortisone have not been as favorable.‡ We have given the corticotropin for longer periods of time and in larger amounts.[27] It may be, however, that the rigid sodium restriction and the generous potassium intake employed in our series is a factor. This could be mediated through the specific effects of these substances in vascular disease or in cellular-extracellular physiology,§ or it may be attributable to morphologic changes in the adrenal cortex produced by these electrolytes. It is known, for example, that rigid restriction of sodium intake and loading with potassium individually and collectively produce a marked increase in the size of the adrenal cortex.‖ Under such circumstances, a given amount of corticotropin may well induce a much greater release of cortical steroids and thereby exert a greater influence upon the disease state.

The beneficial results were not necessarily related to the diuresis induced by corticotropin, since we were able to deliver the extra fluid in the majority of instances in which we tried by other means.

These data support the evidence that corticotropin induces diureses in children with the nephrotic syndrome. The findings in this report indicate that corticotropin did more than deliver edema. There was rapid subsidence of proteinuria and disappearance of abnormal biochemical findings in the majority of the patients. Perhaps more important was the course of events in a patient with multiple

† References 3 and 4.

‡ References 5-26.

§ References 28-30.

‖ References 31 and 32.

recurrences. A. P. illustrates the rapid disappearance of the signs of disease shortly after starting corticotropin, when he had been given long opportunities to do so spontaneously. His recurrences suggest that the remission may be temporary.

Questions relevant to the ultimate outcome in such patients cannot as yet be answered. Our experience indicates that exacerbations do occur but that they are responsive to retreatment. The experience of others [27] emphasizes furthermore that such recurrences may not appear until two or more years have passed. Many of our patients have not been observed for a sufficiently long period to determine whether the treatment regimen will defer or prevent such an outcome. It is not possible to compare the results in these patients with published figures, since the data frequently are not comparable.

Some comments are in order concerning the problems inherent in administering the low-sodium-high-potassium diet. It has been our experience that children tolerate such a regimen quite well and that ingenuity in adding constituents to the diet enhances its acceptability. In part, this may be a manifestation of the sense of well being and increase in appetite following clinical improvement or the use of corticotropin. We have noted similar responses in a larger series of rheumatic fever children under comparable treatment and for a longer time, save that cortisone was given.¶ A copy of the dietary constituents is appended.

The hyponatremia represents a real, though infrequent, hazard in this form of treatment. In our three cases, the low sodium concentrations did not occur as a consequence of renal salt wastage, but such a possibility cannot be excluded. The best precaution, aside from awareness of its possible occurrence, is the frequent measurement of serum sodium concentrations, particularly following paracentesis, diarrhea, or vomiting.

It should be pointed out that the relatively large intake of potassium in these children with renal disease did not produce toxic levels of serum potassium. Again, however, the concentration of this ion should be determined at regular intervals in view of the fact that potassium accumulation can and does occur in renal disease.[35]

¶ References 33 and 34.

SUMMARY AND CONCLUSIONS

All patients are symptomatically improved. Corticotropin therapy is obviously associated with delivery of edema. It seems reasonable to suggest that this treatment also favorably alters the course of the illness. Serious hyponatremia is to be avoided. Treatment seems safe when the patients are adequately followed in the hospital.

Within the limit of the relatively short duration of our follow-up period, 22 (73%) of 30 patients admitted with the nephrotic syndrome are entirely normal; another 4 (13%) are greatly improved and are probably normal, and only 4 (13%) are definitely abnormal. Two of the last four have not been adequately followed. This seems a better record than previously achieved, but a much longer follow-up time is needed before conclusions can be drawn about incidence of recovery.

APPENDIX

Constituents Which May Be Used in a Fifty-Milligram Sodium Diet

Beverages.—Coca-Cola, fruit juices, sodium-free dialyzed milk, water.

Cereals.—Cooked: Cream of Wheat (plain), corn meal, oats (rolled), Ralston, Wheatena. Dry: Puffed Rice, Puffed Wheat, Shredded Wheat.

Fruit.—Any fresh fruit except cantaloupe. Canned: applesauce, apricots, cherries, grapes, peaches, pears, pineapple, prunes, dates, figs, (raw or canned), lemon juice.

Miscellaneous.—Bread (unsalted), butter (unsalted), calcium caseinate (Casec), cinnamon, cloves, cocoa (Hershey), coconut (fresh or unsalted), cornstarch, flour, honey, jelly, macaroni, mustard, Necco Wafers, nuts (unsalted), peanut butter (unsalted), pepper (black), popped corn (unsalted), spaghetti, Spry, sugar, vinegar.

Sample Fifty-Milligram Sodium Diet (2,644 Calories)*

	Gm.	Prot., Gm.	Fat, Gm.	CHO, Gm.	Na, Mg.	K, Mg.
Breakfast						
Orange juice	100	..	..	10	0.5	190
Oatmeal	100	2	..	15	2.0	170
Toast (unsalted)	25	2	..	15	1.0	18
Butter (unsalted)	10	..	10	..	0.5	0.4
Sodium-free milk	240	8	10	12	6.0	320
Calcium caseinate (Casec)	15	13.2	0.3	..	3.0	...
	Subtotal	25.2	20.3	52	12.0	698.4
Dinner						
Potatoes	300	6	..	45	2.4	1,230
Green beans	100	1	..	3	0.9	300
Bread	25	2	..	15	1.0	18
Butter	30	..	30	..	1.5	1.2
Sodium-free milk	240	8	10	12	6.0	320
Coca-Cola	120	..	..	11.4	1.2	62
Tomato salad	50	..	..	..	1.5	115
Orange	100	..	..	10	0.3	170
Canned peach	100	..	..	20	5.0	31
Calcium caseinate	15	13.2	0.3	..	3.0	...
	Subtotal	30.2	40.3	116.4	22.8	2,347.2
Supper						
Bean soup	300	5	..	15	1.0	1,300
Macaroni	300	19.5	1.9	114	1.5	240
Bread	25	2	..	15	1.0	18
Butter	10	..	10	..	0.5	0.4
Sodium-free milk	240	8	10	12	6.0	320
Coca-Cola	120	..	..	11.4	1.2	62
Green peppers	As desired	..	..	..	...	...
Cucumber	50	..	..	..	0.5	115
Banana	100	..	..	20	0.5	420
Pears (raw)	100	..	..	15.8	2.0	100
Calcium caseinate	15	13.2	0.3	..	3.0	...
	Subtotal	47.7	22.2	203.2	17.2	2,575.4
	Total	103.1	82.8	371.6	52.0	5,521.0
	Milliequivalents				2.2	141.5

* Supplemented with iron and vitamins.

Sample Thirty-Milligram Sodium Diet (1,490 Calories)*

	Gm.	Prot., Gm.	Fat, Gm.	CHO, Gm.	Na, Mg.	K, Mg.
Breakfast						
Orange juice	50	..	..	5	0.25	95
Oatmeal	50	1	..	7.5	0.5	85
Toast (unsalted)	12.5	1	..	7.5	0.5	9
Butter (unsalted)	5	..	5	...	0.25	0.2
Sodium-free milk	140	4	5	6	3.0	160
Calcium caseinate	10	8.8	0.2	...	1.0	...
	Subtotal	14.8	10.2	26.0	5.50	349.2
Dinner						
Potatoes	100	2	..	15	0.8	410
Green beans	50	1	..	1.5	0.45	150
Bread	25	2	..	15.0	1.0	18
Butter	20	..	20	...	1.0	0.8
Sodium-free milk	240	8	10	12.0	6.0	320
Coca-Cola	120	..	..	11.4	1.2	62
Tomato salad	50	..	..	...	1.5	115
Orange	100	..	..	10.0	0.3	170
Calcium caseinate	5	4.4	0.1	...	1.0	...
	Subtotal	17.4	30.1	64.9	13.25	1,245.8
Supper						
Bean soup	100	1.23	..	5	0.3	433
Macaroni	150	9.75	0.8	57	0.7	120
Bread	25	2.0	..	15	1.0	18
Butter	10	..	10	...	0.5	0.4
Sodium-free milk	120	4	5	6	3.0	160
Coca-Cola	60	..	..	5.7	0.6	31
Green pepper	As desired	..	..	...	...	...
Cucumber	50	..	..	...	0.5	115
Pears (raw)	50	..	..	7.9	2.0	100
Calcium caseinate	10	8.8	0.2	...	2.0	...
	Subtotal	25.78	16.0	96.6	10.6	977.4
	Total	58.00	56.0	187.5	29.5	2,572
	Milliequivalents				1.3	66

* Supplemented with iron and vitamins.

Vegetables.—Asparagus (fresh or frozen), beans (dry navy, fresh or frozen green, fresh lima, soy), corn on cob (fresh), cranberries, cucumbers, eggplant, lentils, lettuce, onions, peas (fresh), pepper (green), potato, rice, tomato.

Variety has been added to the diet by use of readily available proprietary handbooks describing the use of protein supplements modified when necessary by eliminating those ingredients that would raise the sodium content of the diet above 50 mg.

All foods to be cooked without addition of salt. This diet must be supplemented with iron and vitamins.

REFERENCES

1. Farr, L. E.: Treatment of the Nephrotic Syndrome, Publication 64, American Lecture Series, Springfield, Ill., Charles C Thomas, Publisher, 1951, pp. 3-61.

2. Danowski, T. S.; Greenman, L.; Mateer, F. M.; Peters, J. H.; Weigand, F. A., and Tarail, R.: Clinical and Biochemical Studies During Pregnenolone Therapy, Symposium on Steroids in Experimental and Clinical Practice, New York, Blakiston Company, 1951, p. 311.

3. Boyd, R. I., and Commons, R. R.: Effect of Nitrogen Mustard upon Chronic Glomerular Nephritis, Am. J. Med. **13**:499 (Oct.) 1952.

4. Baldwin, D. S.; McLean, P. G.; Chasis, H., and Goldring, W.: Effect of Nitrogen Mustard on Clinical Course of Glomerulonephritis, A. M. A. Arch. Int. Med. **92**:162-167 (Aug.) 1953.

5. Barnett, H. L.; McNamara, H.; McCrory, W.; Forman, C.; Rapoport, M.; Michie, A., and Barbero, G.: The Effects of ACTH and Cortisone on the Nephrotic Syndrome, Am. J. Dis. Child. **80**:519-520 (Sept.) 1950.

6. Riley, C. M.: The Effect of Adrenocorticotrophic Hormone (ACTH) on Salt and Water Excretion in Children with the Nephrotic Syndrome, Am. J. Dis. Child. **80**:520-521 (Sept.) 1950.

7. Thorn, G. W.; Merrill, J. P.; Smith, S., III; Roche, M., and Frawley, T. F.: Clinical Studies With ACTH and Cortisone in Renal Disease, Arch. Int. Med. **86**:319-354 (Sept.) 1950.

8. Spector, S., and Matthews, L. W.: Effect of Pituitary Adrenocorticotropic Hormone (ACTH) in Children with Nephrosis, Am. J. Dis. Child. **80**: 886-887 (Nov.) 1950.

9. Burnett, C. H.; Greer, M. A.; Burrows, B. A.; Sisson, J. H.; Relman, A. S.; Weinstein, L. A., and Colburn, C. G.: The Effects of Cortisone on the Course of Acute Glomerulonephritis: Report of a Case, New England J. Med **243**:1028-1032 (Dec. 28) 1950.

10. Keith, N. M.; Power, M. H.; Daugherty, G. W., and Keith, H. M.: Some Effects of Cortisone on the Metabolic Disturbance Associated With Glomerulonephritis With Edema, J. Lab. & Clin. Med. **36**:843-844 (Nov.) 1950.

11. Luetscher, J. A., Jr.; Deming, Q. B., and Johnson, B. B.: A Comparison of the Effects of ACTH and Cortisone in Nephrosis, J. Clin. Invest. **30**:658-659 (June) 1951.

12. Farnsworth, E. B., and Ruppenthal, N. C.: Electrophoretic Studies on Serum and Urine Proteins in Nephrosis Treated With ACTH, J. Lab. & Clin. Med. **38**:407-413 (Sept.) 1951.

13. Rapoport, M.; McCrory, W. W.; Barbero, G.; Barnett, H. L.; Forman, C. W., and McNamara, H.: Effect of Corticotropin (ACTH) on Children with Nephrotic Syndrome, J. A. M. A. **147**:1101-1106 (Nov. 17) 1951.

14. Soshea, J. W., and Farnsworth, E. B.: Serum Lipid Analysis in the Nephrotic Syndrome Under ACTH Administration, J. Lab. & Clin. Med. **38**: 414-419 (Sept.) 1951.

15. Hooft, C., and Clara, R.: ACTH and Lipoid Nephrosis, Maandschr. kindergeneesk. **19**:346-360 (Oct.) 1951.

16. Keith, N. M.; Power, M. H.; Daugherty, G. W., and Keith, H. M.: Some Effects of Cortisone on Metabolic Disturbance Associated with Renal Edema: Study of 3 Patients, A. M. A. Arch. Int. Med. **89**:689-707 (May) 1952.

17. Kramer, B.; Casden, D. D.; Goldman, H., and Silverman, S.: Chemical Changes in the Blood in Children with Lipoid Nephrosis Before, During and After Treatment with ACTH (Corticotropin), Fed. Proc. **11**:85-86 (March) 1952.

18. Lenke, S. E., and Berger, H. M.: Abrupt Improvement of Serum Electrophoretic Pattern in Nephrosis After ACTH-Induced Diuresis, Proc. Soc. Exper. Biol. Med. **78**:366-369 (Nov.) 1951.

19. Fellinger, K.; Falkner, R.; Lachnit, V., and Watschinger, B.: Treatment of Nephrotic Syndrome with Cortisone, Deutsches Arch. klin. Med. **199**:481-491, 1952.

20. Fontan; Verger; Martin, and Verin: Treatment of Lipoid Nephrosis by Adrenocorticotropic Hormone, J. méd. Bordeaux **129**:429-431 (May) 1952.

21. Scholten, J., and Schulz, G.: Corticotropin in Symptomatic Treatment of Lipoid Nephrosis, Medizinische **50**:1600-1616 (Dec.) 1952.

22. Iseri, L. T.; Mader, I. J., and Chandler, D. E.: Treatment of the Nephrotic Syndrome, J. Michigan M. Soc. **52**:41-47 (Jan.) 1953.

23. Lange, K.; Slobody, L., and Strang, R.: Treatment of Nephrotic Syndrome with Interrupted ACTH or Oral Cortisone Therapy, Proc. Soc. Exper. Biol. & Med. **82**:315-317 (Feb.) 1953.

24. Lestina, F. A.; Freeman, S., and Wilson, H.: Treatment of the Nephrotic Syndrome with Nitrogen Mustard and ACTH, J. Lab. & Clin. Med. **42**:918 (Dec.) 1953.

25. Philips, I.; Calvin, J. K., and Kagan, B. M.: Nephrotic Syndrome in Children: Observations on the Clinical Course and the Influences of Sulfonamide and Antibiotic Therapy, A. M. A. Am. J. Dis. Child. **85**:451-461 (April) 1953.

26. Farnsworth, E. B.: Studies on Adrenocortical Function in Relation to the Nephrotic Syndrome, J. Clin. Endocrinol. **13**:1169-1191 (Oct.) 1953.

27. Greenman, L., and Danowski, T. S.: Therapy of the Nephrotic Syndrome with Sodium Restriction, Dextran, and ACTH Alone or Combined with Nitrogen Mustard, presented at the 5th Nephrosis Conference, Philadelphia, Nov. 6, 1953, Private Printing for Library Circulation.

28. Danowski, T. S., and Elkinton, J. R.: Exchanges of Potassium Related to Organs and Systems, Pharmacol. Rev. **3**:42-58 (March) 1951.

29. Danowski, T. S.: Newer Concepts of the Role of Sodium in Disease, Am. J. Med. **10**:468-480 (April) 1951.

30. Danowski, T. S.: Fundamental Features of Metabolism of Sodium and Potassium, Am. J. Clin. Path. **23**:1095-1099 (Nov.) 1953.

31. Deane, H. W.; Shaw, J. H., and Greep, R. O.: The Effect of Altered Sodium or Potassium Intake on the Width and Cytochemistry of the Zona Glomerulosa of the Rat's Adrenal Cortex, Endocrinology **43**:133-153 (Sept.) 1948.

32. Badinez, O., and Croxatto, H.: Effect of Potassium Chloride and Sodium Chloride on the Weight of Rat Adrenals, Bol. Soc. biol. Santiago **5**:37-40 (June) 1948.

33. Danowski, T. S.: Treatment of Active Rheumatic Fever with ACTH, Proceedings of 2nd Clinical ACTH Conference, New York, Blakiston Company, Vol. 2, 1951, pp. 640-643.

34. Greenman, L.; Weigand, F. A., and Danowski, T. S.: Prevention of Cardiac Abnormalities in Acute Rheumatic Carditis, J. Clin. Invest. **32**:572 (June) 1953.

35. Danowski, T. S.; Mateer, F. M.; Greenman, L.; Peters, J. H.; Tarail, R.; Clarke, C. E., and Wilkins, D.: Clinical Syndromes with Hyper- or Hypopotassemia, M. Rec. & Ann. **46**:213-217 (Sept.) 1952.

News and Comment

ANNOUNCEMENT

Postgraduate Courses in Pediatrics, Harvard Medical School.—Two postgraduate courses in pediatrics are being offered by the Department of Pediatrics, Harvard Medical School, at Massachusetts General Hospital, in May, 1955. The first, which will be from May 16 through 24, will deal with general pediatric problems. The second, May 25 through 27, will deal with endocrine and metabolic disorders in children and adolescents. Enrollment may be for either course or the total combined course. Those interested should write Courses for Graduates, Harvard Medical School, 25 Shattuck St., Boston.

SOCIETY NEWS

Eighth International Congress of Paediatrics.—As decided at the Seventh International Congress of Paediatrics, in Habana, 1953, the Eighth International Congress of Paediatrics will be held in Copenhagen, in 1956.

The Congress will be opened Sunday, July 22, and closed Friday, July 27, 1956.

It is planned to arrange a scientific and technical exhibition in connection with the Congress.

Further information will be sent to the national pediatric associations and also published in *Acta pædiatrica* and *Helvetica paediatrica acta*.

JAUNDICE IN MUCOVISCIDOSIS (FIBROCYSTIC DISEASE OF PANCREAS)

Report of Four Cases

CHRISTOS D. GATZIMOS, M.D.
and
RICHARD H. JOWITT, M.D., Indianapolis

ALTHOUGH pathologic changes in the liver, varying from fatty metamorphosis to biliary cirrhosis, are not uncommon in fibrocystic disease, jaundice is ordinarily regarded as an unusual symptom of this disease.

From 1922 to Jan. 1, 1954, at the Indiana University Medical Center 6741 autopsies were done. Of these, 3517 were performed on children 15 years of age or less. In this series of autopsies, there were 14 cases of fibrocystic disease of the pancreas, in 4 of which jaundice was a chief complaint. In all four of these cases, confirmatory laboratory evidence of hyperbilirubinemia was obtained. The relative infrequency of jaundice in fibrocystic disease of the pancreas prompted the presentation of the findings in these cases.

REPORT OF CASES

CASE 1.—M. G., a four-day-old white baby girl, had had no bowel movements since birth and was brought to the Medical Center on Feb. 19, 1949, with icterus and signs of intestinal obstruction. Apparently, a sibling died of a similar condition seven years previously.

Positive physical findings were icterus, abdominal distention, and increased bowel sounds. The hemoglobin value was 15 gm. per 100 ml., the white blood cell count was 8100 per cubic milliliter, the van den Bergh reaction was direct positive, and the total bilirubin was 8.3 mg. per 100 ml. Urinalysis was normal. A flat film of the abdomen showed an abnormal gas pattern.

The child was taken to surgery, where the ileum was found to be packed with meconium; the intestine proximal to this was dilated. The meconium was evacuated, and the child was returned from surgery in good condition. During the next few days the child again developed increasing abdominal distention and was reexplored; more meconium was removed from the small intestine, and a side-to-side enteroenterostomy was done. In spite of this, the patient gradually became worse, with increasing signs of respiratory distress, and died on March 7, 1949. During this time the total serum bilirubin had risen to 17.8 mg. per 100 ml. The pathologic findings are summarized in the Table.

CASE 2.—R. L., a white baby boy, aged 6½ months, was admitted to the pediatric service on Jan. 15, 1949, with the chief complaints of jaundice, failure to gain weight, and vomiting his formula. The child was normal until five weeks before admission, when he began to vomit his feedings; one week prior to admission his stools were white and jaundice was first noticed.

Positive physical findings were icterus, a poor state of nutrition, and an enlarged liver palpable 4 cm. below the right costal margin. The hemoglobin was 11 gm. per 100 ml., the red blood cell count was 3,400,000, and the white blood cell count 23,000 per cubic milliliter, with a moderate shift to the left. Bone marrow aspirate was interpreted as normal. The van den Bergh reaction was direct positive, and the total bilirubin, 2.4 mg. per 100 ml. The duodenal contents showed amylase to be 1.8% of the average normal and lipase to be 0.39% of the average normal; proteinase was not found. PA chest x-ray and upper G. I. series were interpreted as normal.

The patient was discharged on Jan. 30, 1949, with a diagnosis of fibrocystic disease of the pancreas. He died two weeks after discharge. An autopsy was performed elsewhere, and the lungs and abdominal organs were sent here for examination. The Table gives a summary of pathologic findings.

CASE 3.—N. P., a 14-month-old white baby girl, was admitted to the pediatric service on May 21, 1948, with the chief complaints of jaundice and cough of five months' duration.

The mother stated that the child had never been well and had eaten poorly since birth. Her stools had frequently been frothy and were always foul smelling. The cough had followed a cold early in the fall and had persisted for eight months. Eleven days before admission jaundice was noted, which apparently had become more intense.

Illustrations were made by the Department of Illustration, Indiana University Medical Center.

From the Departments of Pathology and Medicine of the Indiana University School of Medicine.

Pertinent Pathologic Findings

Case	Age	Sex	Gross Findings	Van den Bergh	Pancreas	Lungs	Liver	Miscellaneous
1	20 days	♀	Icterus; bile ducts grossly present; meconium ileus	Dir. + Ind. 8.3	Cystic fibrosis	Bronchopneumonia; bronchial exudate; emphysema; dil. tracheal glands; congestion	Mucus in intrahepatic biliary ducts; bile plugs in intercellular canaliculi and biliary ducts; fatty metamorphosis; congestion	Dil. Brunner's glands; dil. cervical glands; dil. cystic spaces in gall bladder; cystic duct replaced by many small ducts
2	6½ mo.	♀	Icterus; extrahepatic ducts patent; bronchioles filled with thick exudate	Dir. + Ind. 2.4	Cystic fibrosis	Bronchopneumonia; bronchiolectatic abscesses; dil. tracheal glands	Bile plugs in biliary ducts; ductal hyperplasia; biliary fibrosis	Liver, spleen, r. lung, stomach, pancreas, gall bladder, sent from another hospital
3	14 mo.	♀	Icterus; extrahepatic ducts normal; bronchioles filled with thick exudate	Dir. + Ind. 3.7	Cystic fibrosis	Bronchopneumonia; bronchial exudate; squamous metaplasia of trachea; dil. tracheal glands	Bile plugs in intercellular canaliculi; biliary fibrosis; fatty metamorphosis, slight; congestion	Calcification in renal tubules, minimal
4	4 mo.	♂	Icterus; green hard liver; common and hepatic ducts normal; cystic duct fibrous cord; "white bile" in gall bladder	Dir. 1.8 Ind. 4.8	Cystic fibrosis	Bronchopneumonia; bronchiolectatic abscesses; emphysema; atelectasis	Mucus in intrahepatic biliary ducts; bile plugs in intercellular canaliculi and biliary ducts; ductal hyperplasia; biliary fibrosis; fatty metamorphosis, slight	Dil. Brunner's glands; dil. ducts in parotid with distended mucous cells; dil. cysts in wall of gall bladder

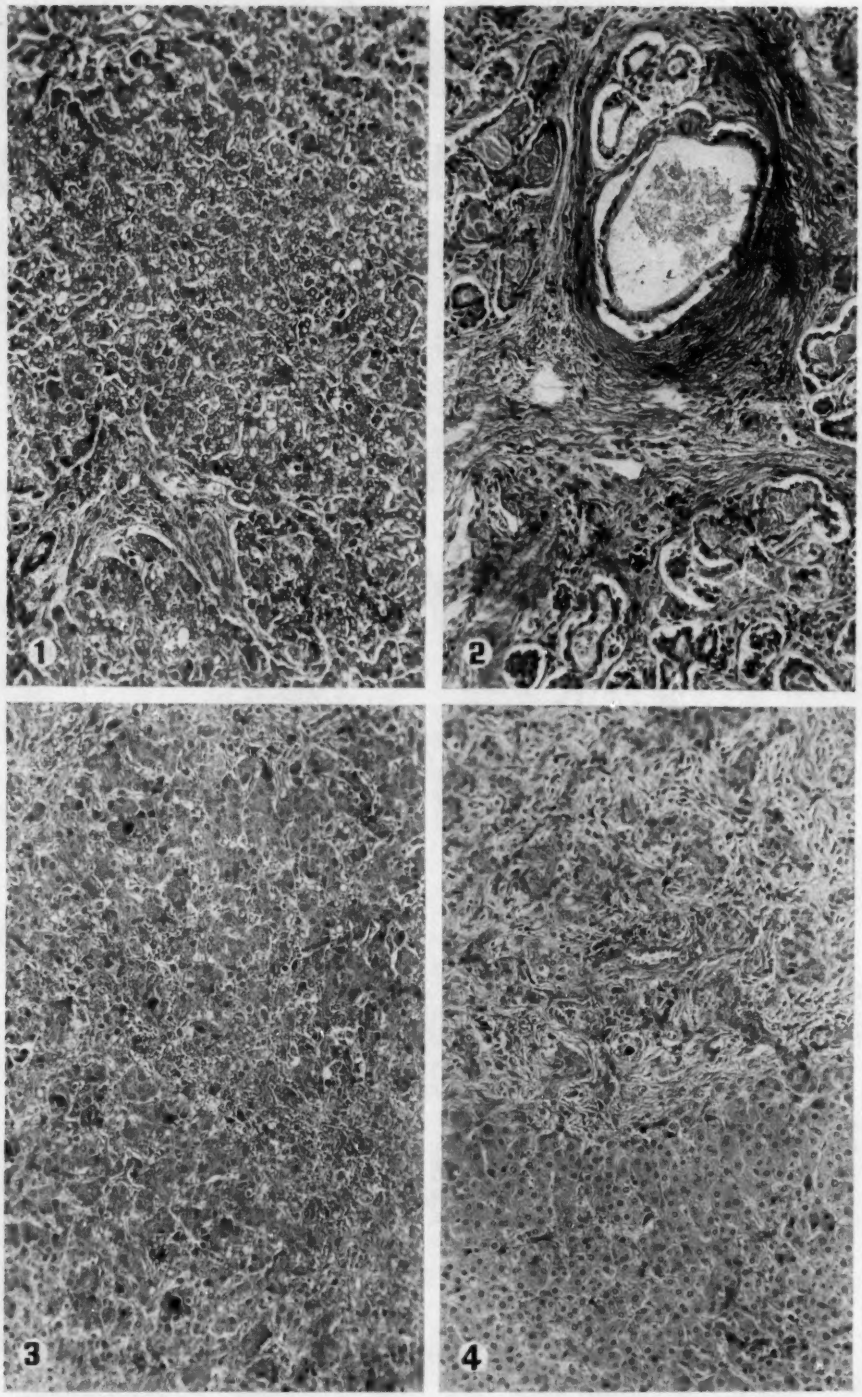


Fig. 1 (Case 1).—Liver (× 180). Fatty metamorphosis and bile plugs in intercellular canaliculi.

Fig. 2 (Case 2).—Pancreas (× 180). Cystic fibrosis.

Fig. 3 (Case 3).—Liver (× 180). Bile plugs in intercellular canaliculi, biliary fibrosis, and slight fatty metamorphosis.

Fig. 4 (Case 4).—Liver (× 180). Mucus in biliary duct, ductal hyperplasia, and biliary fibrosis.

Physical examination revealed icterus, moist rales throughout the lung fields, an enlarged liver palpable 4 cm. below the right costal margin, and foul-smelling yellow-white stools. The hemoglobin was 12 gm. per 100 ml., the red blood cell count 4,400,000, and the white blood cell count 13,000 per cubic milliliter, with a slight shift to the left. The van den Bergh reaction was direct positive and the total bilirubin was 3.7 mg. per 100 ml. The child died 12 hours after admission. The Table gives a summary of pathologic findings.

CASE 4.—S. T., a white baby boy, aged 2 months, was admitted to the pediatric service on June 16, 1953, because of yellow skin, shortness of breath, and cough. The referring physician had also noted a markedly elevated white blood cell count. The child had apparently been well until the onset of the present illness, one week before admission.

The positive physical findings were icterus, an enlarged liver palpable 3 cm. below the right costal margin, and an intermittent relatively nonproductive cough. The hemoglobin was 9.5 gm. per 100 ml., the red blood cell count 2,500,000, and the white blood cell count 21,000 per cubic milliliter, with a marked shift to the left. No evidence of leukemia was found in the peripheral blood or bone marrow on several occasions. The van den Bergh reaction was direct 1.8, indirect 4.8, with a total of 6.6 mg. per 100 ml. The red cell fragility was normal, and the Coombs test negative. Stools were negative for ova and parasites. Chest x-ray was interpreted as normal. On July 16, 1953, the patient had an exploratory laparotomy with a preoperative diagnosis of extrahepatic biliary atresia. At surgery, the cystic duct was seen to be a fibrous strand; the gall bladder was small and white, and did not contain bile. The common and hepatic ducts were not visualized. A biopsy of the liver at this time was interpreted as showing cholangiolitis with obstruction of the bile ducts. The patient was discharged on Aug. 2, 1953.

On Aug. 17, 1953, the child was readmitted because his cough had increased in severity, and he developed intermittent respiratory distress.

Physical examination at this time revealed icterus, a palpable liver, and expiratory wheezes bilaterally, more marked on the right side. His course was ingravescent, and he died on Aug. 26, 1953, in spite of antibiotics and general supportive therapy.

The Table summarizes the pertinent pathologic findings.

COMMENT

In Andersen's [1] series of 49 cases of fibrocystic disease of the pancreas, fatty metamorphosis of the liver was found in 19 cases, biliary cirrhosis was present in 3 cases, and Lænnec's cirrhosis in 1 case. Jaundice was not present as a clinical symptom, though in one of her cases (Case 5) the postmortem observation of "jaundice of the liver" was included as an additional finding.

The important pathologic changes in patients with pancreatic insufficiency were described by Farber.[2] In his 87 cases there was a small number of patients in whom an unfamiliar type of cirrhosis, which appeared to be secondary to intrahepatic biliary obstruction, was found. He states, "Icterus was never observed in these patients."

Fatty metamorphosis of the liver was present in 7 out of a total of 14 cases of fibrocystic disease of the pancreas presented by Baggenstoss and Kennedy.[3] They did not mention the presence of jaundice, nor did Gonce,[4] who discussed the diagnosis and treatment of fibrosis of the pancreas on the basis of 22 cases.

May and Lowe [5] presented the clinical features of fibrosis of the pancreas as manifested by 134 cases. Though they emphasize the pulmonary and cardiac aspects of the disease, they discuss the symptoms under the following headings: meconium ileus, the pancreatic lesion, the pulmonary lesion, and the nutritional state. There is no mention made of the liver lesions or of the presence or absence of jaundice.

Cirrhosis of the liver was present in a 17-year-old white boy who had cystic fibrosis of the pancreas associated with chronic pulmonary disease. This case was reported by Pugsley and Spence,[6] who observed that the van den Bergh reaction remained normal throughout the course of illness. At postmortem examination, the liver was grossly nodular, and microscopically the portal areas showed extensive irregular fibrosis with proliferation of small bile ducts and slight round-cell infiltration.

In his recent book, Bodian [7] presents 116 cases of fibrocystic disease of the pancreas. He found macroscopic evidence of focal fibrosis of the liver in 25% of 62 cases examined postmortem. Out of a total of 50 cases with microscopic section of the liver available for study, 13 showed "simple ductule hyperplasia" in individual portal tracts, and 25

showed focal biliary fibrosis. Despite this large number of cases with liver involvement, Bodian states, "Clinically, no symptoms referable to the liver lesion seemed to be produced during early childhood. In one case, however, a nodular liver was noticed at an operation for appendicitis, and this child was reported later to have developed ascites." * Jaundice was not reported in any case.

The hepatic lesions reported in the Table have been previously described in fibrocystic disease of the pancreas. In Cases 1 and 4, the presence of mucus (mucicarmine-positive material) in the intrahepatic biliary ducts tends to support Farber's theory that the disease is due to an abnormality of the secretion of mucus. It is possible that the pathogenesis of the liver lesion is a primary obstruction of the intrahepatic biliary ducts by the viscid mucus, with a resultant ductal hyperplasia, liver-cell atrophy and biliary fibrosis.

Our four patients, in addition, had jaundice. We are unable to explain the high incidence (4 out of 14) of icterus with these liver lesions in fibrocystic disease of the pancreas. It must be added, however, that most of the patients with this condition, especially the milder cases, are referred back to their local physician after the diagnosis is established. In no case did laboratory or postmortem findings reveal any other cause for the icterus observed. While the jaundice was in infants whose livers showed the most marked changes, there was no correlation between jaundice and duration of the disease process or severity of the other manifestations of the disease.

Typical lesions of the pancreas and liver are shown in the accompanying illustrations.

* Reference 7, p. 152.

SUMMARY AND CONCLUSIONS

Four cases of fibrocystic disease of the pancreas are presented in which persistent jaundice was a predominant clinical sign. Perhaps fibrocystic disease of the pancreas should be considered in the differential diagnosis of icterus in infants.

REFERENCES

1. Andersen, D. H.: Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease: Clinical and Pathologic Study, Am. J. Dis. Child. **56**:344-399 (Aug.) 1938.

2. Farber, S.: Pancreatic Function and Disease in Early Life: Pathologic Changes Associated with Pancreatic Insufficiency in Early Life, Arch. Path. **37**:238-250 (April) 1944.

3. Baggenstoss, A. H., and Kennedy, R. L. J.: Fibrocystic Disease of Pancreas: Study of 14 Cases, Am. J. Clin. Path. **15**:64-70 (Feb.) 1945.

4. Gonce, J. E. Jr.: The Diagnosis and Treatment of Fibrosis of the Pancreas, Wisconsin M. J. **50**:447-450 (May) 1951.

5. May, C. D., and Lowe, C. U.: Fibrosis of the Pancreas in Infants and Children: Illustrated Review of Certain Clinical Features with Special Emphasis on Pulmonary and Cardiac Aspects, J. Pediat. **34**:663-687 (June) 1949.

6. Pugsley, H. E., and Spence, P. M.: Case of Cystic Fibrosis of Pancreas Associated with Chronic Pulmonary Disease and Cirrhosis of the Liver, Ann. Int. Med. **30**:1262-1272 (June) 1949.

7. Bodian, M., Editor: Fibrocystic Disease of the Pancreas: A Congenital Disorder of Mucus Production—Mucosis, London, William Heinemann, Ltd., 1952.

ALLERGENICITY OF MODIFIED AND PROCESSED FOODSTUFFS

V. Soybean; Influence of Heat on Its Allergenicity; Use of Soybean Preparations as Milk Substitutes

BRET RATNER, M.D.
SAMUEL UNTRACHT, M.D., New York
LLOYD V. CRAWFORD, M.D., Memphis
H. JOHN MALONE, M.D., Manchester, Conn.
and
MARY RETSINA, M.D., New York

SINCE the admonition of Duke [1] 20 years ago that soybean might be a prominent cause of allergy, there has been an extraordinary dearth of reports of instances of allergy attributable to its use. This may be explained by the observation of Hill [2] that soybean is a weak antigen.

Hill's idea is corroborated by a report received from a manufacturer of soybean and corn products.* The information came in response to a question relative to allergy encountered among employees. In seven years there have been only 2 cases of soybean allergy of the asthmatic type among 1500 employees who were exposed to soybean fumes and dust in the air. These two persons were skin tested and found sensitive to soybean flour. Attacks of asthma were precipitated by contact with soybean dust. It was further asserted that two or three persons per year attributed skin rashes to the handling of soybean flour. In these latter cases, however, the skin tests were invariably negative and the so-called skin allergy turned out to be either prickly heat or fungous infection. During the war a large amount of packaged soy flour was used, and the report noted an absence of sensitization from this source.

A report from another manufacturer stated that allergy to soy flour has been so infrequent that it is considered of no importance.†

Despite the paucity of cases of soybean sensitivity in man and despite the demonstration of the innately weak antigenicity of soybean for the guinea pig, to be reported shortly,[3] and in view of the fact that soybean preparations are used as substitutes for milk in the diet of milk-sensitive children, it appeared important to us to determine the potency of soybean as an allergen in the human subject. Simultaneously we sought to investigate what influence heat has on its allergenicity.

This particular study of soybean allergenicity could not have been made without a good antisoybean human serum. Because of the paucity of soybean-sensitive cases and the fact that we had none in our practice, we made inquiries among our colleagues to discover whether any were available. The response was uniformly negative, with one exception. Dr. L. E. Seyler, of Dayton, Ohio, reported to us that he had a patient in whom he had found a good soybean antibody titer. He obtained a quantity of serum from this patient for us.

The donor of the soybean antibody serum (H. S.) was an adult woman who in 1941 came to see Dr. Seyler with a history of shock and collapse after eating Bologna containing soybean filler. She was found to be skin-sensitive to soybean and several other cereal foods and some inhalants.

Formerly Research Fellows in Pediatric Allergy (Drs. Crawford, Malone, and Retsina).

This study was supported in part by a grant from the Playtex Park Research Institute.

From the Departments of Pediatrics and Immunology, New York Medical College and Flower and Fifth Avenue Hospitals, and the Pediatric Division of Sea View Hospital, New York.

* Information obtained from F. G. Irwin, M.D., Medical Director, A. E. Staley Manufacturing Co., Decatur, Ill.

† Information obtained from H. A. Olendorf, Manager Soy Flour Department, Spencer Kellogg & Sons, Inc., Decatur, Ill.

She presumably had become sensitized from contact with soybean dust emanating from a soybean processing plant opposite her home. She had had to move from the house because the soybean dust in the air caused abdominal distress and asthma. She had not had an asthmatic attack, prior to this last one, in the three to four years since she moved from the environment of the plant.

EXPERIMENTAL DATA

Materials

Soybean Antibody Serum (H. S.).—This was obtained from Dr. Seyler's patient.

Soybean Extract (SBE).—The extract used for testing is the same as that described in Paper VI of this series.[3]

Soybean Flour.—The flour used for feeding experiments is Special X Brand, manufactured by Spencer Kellogg & Sons, Inc., Decatur, Ill.

Soybean Preparations.—The following preparations were used (Table 1).‡

Soybean Preparation A: Liquid Mull-Soy, the standard material produced by the Borden Company for infant feeding. It is prepared by making a liquid mix of soybean flour at 165 F for 20 minutes. This is cooled to 60 F and retorted at 260 F for 60 minutes.

Soybean Preparation B: Soybean liquid mix, unheated, spray-dried.

Soybean Preparation C: Soybean liquid mix, heat treated for a short time. It is mixed at 150 F and then sterilized at 300 F for 25 seconds.

Soybean Preparation D: Preparation C spray-dried at 175 F.

Soybean Preparation E: Soybean liquid preparation mixed at 180 F for 10 minutes, cooled to 150 F, reheated to 205 F for 4 minutes and then spray-dried.

Soybean Preparation F: A liquid soybean product on the market, of unknown preparation.

Soybean Preparation G: A powdered soybean product on the market, of unknown preparation.

Soybean Preparation H: Two brands of soy oil on the market, Crude Soy Oil (Borden) and Soy Oil (Kraft).

Soybean Preparation I: A soy sauce on the market (La Choy Sauce), of unknown preparation.

Soybean Preparation J: A corn soya cereal on the market, of unknown preparation.

‡Dr. J. F. Muller, Director of Research, Prescription Products Division, The Borden Company, furnished us with Soybean Preparations A through E.

Table 1.—*Soybean Preparations from Liquid Mix*

Preparation	Heat Treatment	Time	Other Treatment
A (liquid)	165 F	20 min.	.....
	Cooled to 60 F		
	260 F	60 min.	
B	Unheated	.....	Spray-dried
C (liquid)	Mixed at 150 F		.....
	300 F	25 sec.	
D	Mixed at 150 F		Spray-dried
	300 F	25 sec.	at 175 F
E	180 F	10 min.	Spray-dried
	Cooled to 150 F		
	205 F	4 min.	

Methods

The anti-soybean serum (H. S.) was passively transferred to normal recipients, and the prepared sites were tested directly with soybean extract to determine the presence of antibodies.

The dual ingestion passive transfer test has been described in detail in a previous article.[4] The purpose of the experiment is to determine whether the modification of a food by various methods alters its allergenicity. The method is essentially the testing by oral route of normal recipients passively sensitized in the skin of the arm with antibody-containing serum. The recipient ingests the modified food. If he shows no reaction, he then ingests the unmodified or native food.

Children at Sea View Hospital were injected intradermally with H. S. serum in two sites on each forearm. Twenty-four to 72 hours later, various soy-containing foods were given by mouth before breakfast. Effects were observed on the passively sensitized arm sites during the next 1 to 24 hours. When no skin reaction was noted, the recipient drank a suspension of soybean flour in water. The dermal reactions of the prepared sites were then watched. The absence of any reaction following the ingestion of processed soy-containing foods and the subsequent appearance of a positive reaction following the ingestion of a raw soy flour suspension indicates an altered allergenicity of the processed product or an inability of the modified material to traverse the intestinal wall.

Occasionally we would encounter a nonreactive passive transfer recipient. Since experiments on such persons were negative throughout and would add nothing to the solution of the problem at hand, they have been omitted from the protocols.

RESULTS

Presence of Soybean Antibodies in H. S. Serum

Before the serum obtained from Dr. Seyler's patient was used for experimentation, the presence of soybean antibodies was determined by utilizing eight volunteer staff members as recipients. Two sites on each

TABLE 2.—*Dual Ingestion Passive Transfer Test, Soybean Preparation A* *

Recipients, No.	Preparation A		Soy Flour	
	Period Observed, Hr.	Reaction	Period Observed, Hr.	Reaction
14	3½	Negative	3	Positive
4	24	Negative	1	Positive
Infant	1½	Negative	½	Positive

* Passively sensitized children ingested 4 oz. Preparation A in 4 oz. water; infant ingested 2 oz. Preparation A in water. Control ingestion of soy flour, 3 tablespoonfuls in 6 to 8 ounces of water. Unless otherwise specified this dose of soy flour was used throughout the experiments. The infant ingested 2 teaspoonfuls flour in water.

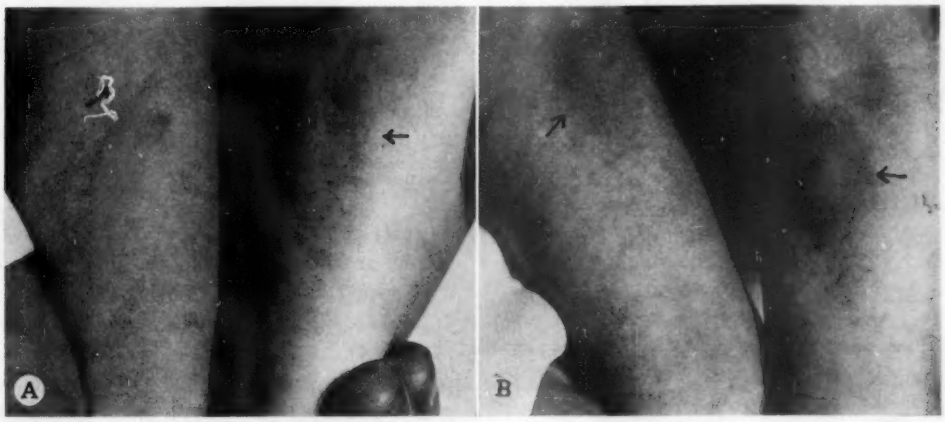
forearm of each subject were injected with 0.1 cc. H. S. serum. Twenty-four hours to 1 week later, each was directly tested with 0.02 cc. soybean extract 1 : 1000 at the site of passive sensitization. All gave positive reactions. Unsensitized control sites were negative in all recipients. These findings were accepted as evidence for the presence of soybean antibodies in the donor serum (H. S.).

DUAL INGESTION PASSIVE TRANSFER TESTS

Experiment I, Soybean Preparation A (Table 2).—Eighteen children up to 12 years of age and 1 infant were passively sensitized with H. S. serum in doses of 0.5 to 0.1 cc. From 24 to 72 hours after H. S. serum injections, the subjects drank 4 oz. of liquid Preparation A mixed with 4 oz. of water. The infant drank 2 oz. of this preparation. No reactions ensued.

Each child was then given 4 tablespoonfuls of soy flour suspended in a glass of water (6 to 8 oz.). The infant drank 2 teaspoonfuls of soy flour thinly suspended in water. In all instances positive reactions appeared at the passively sensitized sites. These reactions consisted of 1 to 2 cm. wheals and erythema 2 to 4 cm. in diameter.

The reactions were noted within 10 to 15 minutes and reached a maximum size in ½ to 1½ hours. Two of the children developed only an erythema during 2½ hours of observation. In seven instances serum sites tested by direct intracutaneous injection three weeks previously flared up with positive reactions.



Dual ingestion passive transfer test. Normal infant, one year of age, passively sensitized in each forearm at point of arrows 24 hours before test. *A*, absence of reaction one and one-quarter hours after ingestion of 2 oz. soybean Preparation A; *B*, reaction three-quarters of an hour after ingestion of 2 teaspoonfuls of raw soy flour.

Thus it may be noted (Table 2) that 19 recipients, negative with Preparation A, had positive reactions with soy flour. On the basis of previous experiences with the dual ingestion method, this indicated to us that Preparation A either was hypoallergenic or had been altered into a form incapable of traversing the intestinal wall. The unaltered soybean readily passed through the intestinal wall into the blood stream.

The Figure depicts the results of the dual ingestion passive transfer test, showing the

TABLE 3.—*Dual Ingestion Passive Transfer Test, Soybean Preparation B* *

Recipients, No.	Preparation B: Period Observed, Hr.	Preparation B: Reaction	Soy Flour: Period Observed, Hr.	Soy Flour: Reaction
7	2	Positive	1½	Positive
3	2	Positive	3	Negative
1	2	Positive	Not done	.....
1	24	Negative	1½	Positive

* Passively sensitized children ingested 3 to 4 tablespoonfuls of Preparation B suspended in 6 to 8 oz. of water.

absence of any reaction at the point of passive sensitization when Preparation A was ingested and a definite reaction when raw soy flour was later used as a challenge ingestion.

Experiment II, Soybean Preparation B (Table 3).—In this series another soybean preparation, not subjected to heat but spray-dried, was used in a test similar to Experiment I.

Three to 4 tablespoonfuls suspended in 6 to 8 oz. of water were given to each of 12 children before breakfast. These children had been sensitized with H. S. serum 24 hours previously. A positive reaction occurred in

TABLE 4.—*Dual Ingestion Passive Transfer Test, Soybean Preparation C* *

Recipients, No.	Preparation C: Period Observed, Hr.	Preparation C: Reaction	Soy Flour: Period Observed, Hr.	Soy Flour: Reaction
6	1¾	Positive	1½	Positive
2	3½	Negative	1½	Positive
3	24	Negative	1¼	Positive

* The passively sensitized children drank 4 oz. of Preparation C mixed with equal parts of water.

11 instances, which showed this unheated spray-dried material to be allergenic.

In one recipient no reaction was noted during the 24-hour period following the ingestion of the spray-dried preparation. The child demonstrated a dermal reaction of 1 cm. erythema after the ingestion of soy flour.

The challenge dose of soy flour was given to 10 of the remaining 11 children. Seven of them revealed positive dermal reactions within one and one-half hours. Three children who had previously shown large positive reactions to the spray-dried preparation failed to react to the soy flour challenge dose. Their dermal reactivity may have been exhausted as a result of the earlier reaction.

Experiment III, Soybean Preparation C (Table 4).—Eleven children were passively sensitized with H. S. serum. They then drank 4 oz. of Preparation C mixed with equal parts of water. Within one and three-quarters hours, six of the children developed typical positive dermal reactions consisting of erythema and wheal. The reactions obtained with soy flour were appreciably larger in each instance. The five recipients who failed

TABLE 5.—*Dual Ingestion Passive Transfer Test, Soybean Preparation D* *

Recipients, No.	Preparation D: Period Observed, Hr.	Preparation D: Reaction	Soy Flour: Period Observed, Hr.	Soy Flour: Reaction
5	1½	Positive	1¼	Positive
4	24	Negative	1¼	Positive

* The passively sensitized children ingested 3 tablespoonfuls of Preparation D in 6 to 8 oz. of water.

to react to Preparation C all had positive dermal reactions following the ingestion of 3 tablespoonfuls of soy flour.

Experiment IV, Soybean Preparation D (Table 5).—Nine children previously prepared with antisoy serum (H. S.) were given 3 tablespoonfuls of Preparation D in 6 to 8 oz. of water. Within one and one-half hours, five of the recipients showed dermal reactions with wheals of about 0.5 cm. and erythema 1.5 to 2.0 cm. After 24 hours all nine children were given a mixture of 3 tablespoonfuls of raw soy flour suspended in 6 to 8 oz. of water. Positive dermal reactions were noted in all.

Thus, this Preparation D is allergenic.

TABLE 6.—*Dual Ingestion Passive Transfer Test Soybean Preparation E* *

Recipients, No.	Preparation E: Period Observed, Hr.	Preparation E: Reaction	Soy Flour: Period Observed, Hr.	Soy Flour: Reaction
9	2	Negative	1½	Positive
9	5	Negative	½	Positive

* The passively sensitized children ingested 3 tablespoonfuls of Preparation E in 6 oz. of water.

TABLE 7.—*Dual Ingestion Passive Transfer Test Soybean Preparation F* *

Recipients, No.	Preparation F		Soy Flour	
	Period Observed, Hr.	Reaction	Period Observed, Hr.	Reaction
7	1½	Positive	2½	Positive
4	3	Negative	1¼	Positive
2	24	Negative	1¼	Positive

* The passively sensitized children each ingested 4 oz. of Preparation F in 4 oz. of water.

Experiment V, Soybean Preparation E (Table 6).—In passive transfer tests with Preparation E, none of 18 recipients reacted to its ingestion. When these subjects were challenged with soy flour by ingestion, all gave positive reactions.

Experiment VI, Soybean Liquid Preparation F (Table 7).—Thirteen children, passively prepared with H. S. serum, each drank a mixture of 4 oz. of Preparation F in 4 oz.

TABLE 8.—*Dual Ingestion Passive Transfer Test Soybean Preparation G* *

Recipients, No.	Preparation G		Soy Flour	
	Period Observed, Hr.	Reaction	Period Observed, Hr.	Reaction
9	1	Positive	1¼	Positive
3	3	Negative	¾	Positive

* The passively sensitized children each ingested 3 tablespoonfuls Preparation G in 6 oz. of water.

of water. Within one and one-half hours, seven reacted positively. When challenged with soy flour ingestion, all recipients demonstrated positive reactions.

Experiment VII, Soybean Powdered Preparation G (Table 8).—Twelve additional recipients drank a mixture of 3 tablespoonfuls of Preparation G in 6 oz. of water. Of these, nine showed strongly positive reactions at the passively sensitized sites within one hour. All manifested positive reactions when challenged by ingestion of soy flour.

Experiment VIII (Table 9).—Three products derived from soybean were each tested for antigenicity on children passively sensitized with H. S. serum.

Eight children drank 1½ to 2 oz. of soy oil (Preparation H). No reactions ensued at the prepared skin sites. All gave positive reactions when challenged by ingestion of soy flour.

Five children drank 4 teaspoonfuls of soybean Preparation I mixed in water. There were no reactions, but all reacted positively to challenge ingestion of soy flour.

Nine children ate 1½ oz. (dry weight) of Preparation J moistened in water. No reactions ensued. All reacted positively to soy flour ingestion.

SOYBEAN IN RELATION TO MILK ALLERGY

Evaporated or heated milks, which ordinarily serve as adequate substitutes in cases of sensitivity to the lactalbumin fractions of cow's milk,[5] completely fail in cases of milk allergy that are profoundly sensitive to the casein fraction. It has been found that casein is not reduced in allergenicity by exposure to heat. Casein is also species nonspecific, and therefore milk from one species cannot be substituted for another in the casein-sensitive case. In such instances, the most valuable milk substitute is derived from soybean.

As an illustration, we would like to cite the case of an infant 1 year and 4 months of age who suffered from marked asthma and who was exquisitely sensitive to the milk proteins. The skin tests revealed the following reactions: whole milk 2+, lactalbumin 1+, specially purified lactalbumin 0, beef 0,

TABLE 9.—*Dual Ingestion Passive Transfer Test with Soybean Preparations H (Soy Oil), I (Soy Sauce), and J (Corn Soya Cereal)*

Recipients, No.	Preparation Tested	Period Observed, Hr.	Reaction	Soy Flour	
				Period Observed, Hr.	Reaction
4	H	1½	Negative	2¼	Positive
4	H	24	Negative	1¼	Positive
5	I	1¼	Negative	1½	Positive
9	J	3	Negative	1	Positive

beef serum 0, casein 2+. American Gorgonzola, Limburger, Parmesan, Roquefort, and Swiss cheeses all gave positive reactions.

It will be noted that this child had a negative reaction to beef protein and beef serum, which indicates an absence of sensitivity to the lactoglobulin fraction. He gave a positive reaction to the regular lactalbumin protein fraction but a negative reaction to a specially purified lactalbumin. He did, however, give a 2+ reaction to whole milk and to casein. He likewise reacted to six cheeses with which he had been tested. These dermal reactions demarcate this child as one who is casein-sensitive.

An interesting fact in his history is that during the period of gestation the mother consumed 2 qt. of milk a day, besides eating other milk-containing foods. This points to the possibility of an acquired active sensitization in utero.[6]

The case was also complicated by sensitivities to certain other foods and to some inhalants. All have been either removed from his environment or modified to the point of tolerance. This boy has been observed for more than a year. He has been unable to tolerate any form of milk, including evaporated and boiled milks, and has thrived on the milk substitute Mull-Soy.

In our judgment this case demonstrates the importance of procuring an adequate substitute for milk for a person exquisitely sensitive not only to the albumin fractions but, more specifically, to the casein fraction of cow's milk. In the treatment of such a case it is necessary to eliminate all milk proteins, not only as such but even in modified forms and as found in the preparation of foods. A properly treated soybean preparation proved in this case to be a satisfactory substitute.

COMMENT

That soybean antigen can regularly traverse the normal intestinal wall has been demonstrated.

Liquid Preparation A, heat-treated to 165 F for 20 minutes and retorted at 260 F for 60 minutes was hypoallergenic, as was this preparation when spray-dried (Preparation E). On the other hand, the unheated spray-dried Preparation B, the liquid heated for a short time (Preparation C) and this latter preparation spray-dried (Preparation D) were all allergenic.

Liquid and spray-dried soybean preparations used for infant feeding (Preparations F and G), available on the market but of unknown preparation, were allergenic.

Soybean oil, soybean sauce, and a corn soya cereal were nonallergenic.

The hypoallergenicity of the heated protein cannot always be attributed to a change in the protein molecule. Boiling may coagulate the protein and thus reduce its solubility in the intestinal tract. The insoluble protein cannot traverse the intestinal wall and thus cannot enter the circulation to reach the site of antibody fixation.

In the light of the generally poor antigenicity of soybean and the further reduction in allergenicity that stems from heat processing, we believe that certain soybean preparations can be used as milk substitutes in the prophylaxis of infantile allergy, as advocated by Glaser and Johnstone.[7] This type of preparation cannot in and of itself be the direct cause of any allergic manifestations. From the allergic standpoint, therefore, a proper soybean preparation is an ideal hypoallergenic foodstuff.

CONCLUSIONS

Soybean is innately a weak allergen.

Untreated native soybean protein readily passes through the intestinal wall in an unchanged state but, despite this, is the cause of allergic manifestations in only rare instances.

In the few cases of sensitivity to soybean reported in the literature, sensitization was established through prolonged inhalation of soybean dust rather than through ingestion.

The proper processing of soybean protein by adequate heat in the presence of moisture reduces whatever allergenic properties are present.

Inadequate heat and direct spray-drying of the unheated liquid soybean mix does not reduce its allergenicity to any noticeable degree.

Soybean protein adequately heated in the presence of moisture and then spray-dried is hypoallergenic.

Within the limits of our experiments, we found that soybean oil, soybean sauce, and a corn soya cereal were devoid of allergenicity.

From the allergic standpoint, a properly modified soybean preparation is an ideal hypoallergenic substitute in the case of a person sensitive to the casein fraction of milk.

REFERENCES

1. Duke, W. W.: Soy Bean as a Possible Important Source of Allergy, J. Allergy **5**:300 (March) 1934.

2. Hill, L. W.: The Production of Nonetiological Skin Hypersensitivity to Foods by Natural Means in Atopic Persons, J. Allergy **13**:366 (May) 1942.

3. Ratner, B., and Crawford, L. V.: Allergenicity of Modified and Processed Foodstuffs: VI. Soybean; Anaphylactogenic properties, to be published.

4. Ratner, B.; Untracht, S., and Collins-Williams, C.: Allergenicity of Modified and Processed Foodstuffs: I. The Use of a Dual Ingestion Passive Transfer Test to Determine the Allergenicity of Foodstuffs in Man, Ann. Allergy **10**:675 (Nov.-Dec.) 1952.

5. Ratner, B., and Gruehl, H. L.: Anaphylactogenic Properties of Milk, Am. J. Dis. Child. **49**:287 (Feb.) 1935.

6. Ratner, B.: A Possible Causal Factor of Food Allergy in Certain Infants, Am. J. Dis. Child **36**:277 (Aug.) 1928.

7. Glaser, J., and Johnstone, D. E.: Prophylaxis of Allergic Disease in the Newborn, J. A. M. A. **153**:620 (Oct. 17) 1953.

OBSERVATIONS ON TRICHINOSIS

Report of a Community Outbreak

LELABELLE C. FREEMAN, M.D.
FREDERICK J. BRADY, M.D.
ALTHEA D. KESSLER, M.D.
and
ROLAND B. SCOTT, M.D., Washington, D. C.

CLINICAL trichinosis is not common in the United States, even though trichinae are found in the diaphragm (muscle) of about 16% of bodies coming to autopsy. Between 1842 and 1943, over 12,000 clinical cases were reported in the United States.* The discrepancy between the large number of persons infected and the small number of persons that are diagnosed as having trichinosis can be attributed, in part, to a "dilution factor" by which infected meat is diluted with uninfected meat in modern packing plants.

The consumer who prepares his own pork is, of course, not protected by this dilution factor. The outbreak reported here is such an instance. This outbreak illustrates several diagnostic factors that are worth reporting.

BACKGROUND

F. H., a farmer, resided in rural Virginia, a few miles from the District of Columbia. He lived in a community consisting of 21 persons occupying four houses. Customarily hogs are slaughtered each fall and the meat distributed among the 21 residents.

Hogs were raised on garbage trucked in from nearby Virginia, except for a month prior to slaughter, when they were fed grain to give the meat a better quality. Most of the meat was salted down, but scraps were seasoned and ground into sausage. During the preparation of the sausage the children were prone to eat the meat raw.

DEVELOPMENT OF OUTBREAK

Attention was first called to the possibility of trichinosis when several children became seriously ill and a neighbor volunteered the information that several of his hogs had died of unknown causes. Although the exhumed carcasses of these hogs showed no trichinae, meat from a previously slaughtered animal showed two dead trichinae per gram of tongue tissue. Specimens from a recently slaughtered hog of P. H. were examined with the following results:

Tissue	Press Preparation (Larvae/Gm.)	Digestion Preparation (Larvae/Gm.)
Extraocular muscle	226	.....
Masseter muscle	222	.....
Tongue	174	86.46
Shoulder	20	39.38
Ham	60	15.94
Miscellaneous pieces	62	28.13

A hog was slaughtered on Dec. 12, and the meat was eaten on Dec. 14. Three days later L. H. (Table 1) complained of malaise and a soreness of the left arm lasting two days. Symptoms developed in 11 additional members of the community during the next few weeks. Two persons had signs of trichinosis but no symptoms, and the remaining seven were clinically free of the disease.

Table 1 represents a tabulation of the outstanding symptoms and findings in the 21 residents.

HOSPITALIZED CASES

CASE 1.—A. H., an 8-year-old boy, entered Freedmen's Hospital Dec. 23, with a history of having been well until Dec. 18, when he suddenly developed frontal headache, generalized muscular pains, particularly in the legs, abdominal discomfort and distention, and muscular weakness. The muscular weakness so debilitated the boy that he became

From the Department of Pediatrics of Howard University College of Medicine, the Pediatric Service of Freedmen's Hospital and the Microbiology Institute of the National Institutes of Health.

Dr. Brady is presently International Health Representative, U. S. Public Health Service, formerly Assistant Chief, Laboratory of Tropical Diseases, National Institutes of Health.

*Wright, W. H.: Personal communication to the authors.

unable to walk one day after onset. There was a history of drinking spring water and unpasteurized milk. At the time of admission, two other members of the family were suffering from an undiagnosed illness with similar symptoms.

Physical examination revealed a well-developed, well-nourished, well-oriented boy sweating profusely. His temperature was 103 F, respiration rate was 36 to 40 per minute, and pulse rate was 125 per minute. The positive findings were moderate prostration, rapid shallow breathing, positive head drop, stiffness of the back (poker back), inability to sit erect without assistance, and scattered fine crackling rales in the chest but no consolidation. The extremities appeared normal, but practically all voluntary movement was absent, and passive motion caused extreme tenderness and pain. He stammered when he spoke, and the deep reflexes were markedly diminished.

Laboratory data showed R. B. C. 3,000,000; hemoglobin 85%; W. B. C. 5,550, with neutrophiles 82%, lymphocytes 16%, monocytes 2%. The urine was negative for glucose and albumin. Blood cultures and the blood Wassermann test were negative.

TABLE 1.—*Clinical Course of all Residents in the Involved Households*

Patient	Age, Yr.	Sex	Date of Onset	Symptoms	Pork Ingestion	Bed Confined	W. B. C.	Eos., %	Skin Test	Precipitin Test	Trichinosis Diagnosed
					Household 1						
F. H.	54	M	1/17	Stiffness	Yes	No	10,000	1	Neg.	Neg.	No
M. H.	48	F	1/3	Headache Weakness Facial edema Hoarseness Fever Dyspnea Tachycardia Dependent edema	Yes	Yes	5,700	52	Neg.	Neg.	Yes
Ro. H.	15	M	12/19	Fever Muscle pain Abdominal pain Weakness Prostration	Yes	Yes	43,350	62	Pos.	1:640	Yes
Re. H.	13	M	12/25	Headache Weakness Fever Stiffness Orbital edema Prostration	Yes	Yes	9,950	34	Pos.	1:1280	Yes
Ru. H.	13	M	12/18	(Case 2)	Yes	Hosp.	12,200	19	Pos.	1:640	Yes
L. H.	10	F	12/17	Malaise Stiffness	Yes	No	18,600	54.5	?	1:2560	Yes
A. H.	8	M	12/18	(Case 1)	Yes	Hosp.	5,500	0	Pos.	1:2560	Yes
D. H.	6	M	12/25	Fever Abdominal pain Weakness	Yes	No	12,700	36	Neg.	1:1280	Yes
Ri. H.	4	M	12/25	Fever Abdominal pain Stiffness Weakness Prostration Tachycardia Listlessness	Yes	Yes	10,450	13	Neg.	Not done	Yes
					Household 2						
G. H.	24	M	12/20	Fever Stiffness Muscle pain Facial edema Prostration	Yes	Yes	.....	69	Not done	Not done	Yes
V. H.	19	F	12/26	Neck soreness	Yes	No	9,550	7	Neg.	Not done	No
P. H.	2	F	12/22	Fever Weakness Facial edema	Yes	Yes	13,500	17	Pos.	Not done	Yes
A. H.	6 mo.	F	.....	None	No	No	.....	..	....	Not done	No
					Household 3						
C. H.	24	M	.....	None	Yes	No	10,550	2	Not done	Neg.	No
D. H.	18	F	?	Headache Shoulder pain	Yes	No	13,150	56	Pos.	1:320	Yes
Do. H.	2	F	.....	None	Yes	No	6,550	0	Not done	Not done	No
					Household 4						
J. M.	39	M	.....	None	Yes	No	8,650	7	Neg.	Neg.	No
M. M.	31	F	.....	None	Yes	No	15,750	58	Pos.	1:320	Yes
Jo. M.	14	M	12/29	Facial edema Headache	Yes	No	15,550	43	?	1:2560	Yes
L. M.	8	F	.....	None	Yes	No	14,000	59	?	1:160	Yes
S. M.	3	F	.....	None	No	No	6,750	6	Neg.	Not done	No

A lumbar puncture revealed normal chemical, bacteriological, cellular, and dynamic findings. Agglutinations for typhoid and Salmonella paratyphi A and B were all negative. The x-ray of the chest revealed bilateral congestion and an enlarged hilus shadow.

Influenza, rheumatic fever, typhoid fever, poliomyelitis, and trichinosis were considered as diagnostic possibilities. The chest became normal in five days, but the patient did not appear improved. A hemogram on the sixth hospital day showed 27% of the leucocytes to be eosinophiles. The intradermal test for trichinosis was positive. The precipitin test for trichinosis was positive in dilution of 1:2560. A second spinal tap on the seventh hospital day showed 40 lymphocytes per cubic millimeter. A soft systolic murmur developed two weeks after admission, but several electrocardiograms were normal. The speech impediment disappeared in one month. The muscular pain cleared in five weeks with mild residual muscular atrophy.

A muscle biopsy performed in the fifth week of illness revealed no trichinae. The patient was discharged from the hospital eight weeks after onset of illness with no complaints.

CASE 2.—Ru. H., the 13-year-old brother of A. H., entered Freedmen's Hospital Dec. 28, five days after A. H., complaining of generalized muscular pain, fever, extreme weakness, and diarrhea followed by constipation.

Physical examination revealed an acutely ill child who was too weak to turn over in bed. His temperature was 102 F. The skin was moist with droplets of perspiration. The chest and heart were normal to examination. The abdomen was distended, and epigastric tenderness was present. The deep tendon reflexes were absent. Muscular power was markedly diminished. There was generalized hyperesthesia present, making it difficult to appraise a suggestively positive Kernig sign.

Laboratory data: R. B. C. 4,750,000; W. B. C. 12,000, with neutrophiles 75%, lymphocytes 5%, basophiles 1%, and eosinophiles 19%. The urine contained erythrocytes and 2 + albumin. The spinal fluid pressure was 160 mm. of water, and 5 lymphocytes per cubic millimeter were present. The skin test for trichinosis was positive, and the precipitin test was positive in a dilution of 1:640.

One week after admission, an aortic systolic murmur was heard, and the blood pressure was 150/90. He also developed a generalized vesicular rash and slight edema about the eyes. The patient improved slowly and was discharged in good condition after four week's hospitalization.

COMMENT

There is no doubt in our minds that the cases under investigation were trichinosis because of the history of ingestion of infected meat, the clinical features of the disease in 12 persons, eosinophilia in 14, positive skin tests in 7, and positive precipitin tests in 10.

In this series of 14 cases, the outstanding symptoms in order of occurrence were as follows, with 2 cases being asymptomatic:

fever	9 cases
weakness	8 cases
headache	6 cases
stiffness	5 cases
edema	5 cases
muscle pain	5 cases
prostration	5 cases
abdominal pain	4 cases

These observed symptoms follow the order of frequency reported in most outbreaks, except for the absence of the early symptoms referable to the gastrointestinal tract (nausea, vomiting, and diarrhea) which occur in about one-third of symptomatic cases. It is noteworthy that malaise and prostration occurred as early as three or four days after the alleged first ingestion of the infected meat. Weakness and fever were the outstanding complaints in this epidemic. Both of these are generally related to the severity of the disease. Muscular pain appeared early and was followed by stiffness which soon gave way to extreme muscular weakness. The muscles were neither spastic nor flaccid but had a doughy consistency. Laboratory data are summarized in Table 2.

Blood cell counts done in the second or third week of illness showed leucocytosis

TABLE 2.—*Summary of Laboratory Findings*

Type of Case	Total No. Cases	Leucocytosis	Eosinophilia	Skin Test		Precipitin Test	
				Positive	Negative or Doubtful	Positive	Negative or Doubtful
Severe	8	4	8	5	2	4	1
Mild	4	4	4	1	3	4	0
Asymptomatic	2	2	2	1	1	2	0
Noninfected	7	1	0	0	4	0	3

(over 10,000 cells per cubic millimeter) in 10 of the 14 cases. Eosinophilia ranging from 13% to 69% was present in all cases. Three children had Ascaris and one had whipworm infestation, which may have mildly influenced the eosinophilia. There was no correlation between the height of the eosinophile count and the severity of the disease. In one of the hospitalized patients, eosinophilia was absent until the second week of the disease. It has been observed [1] that eosinophilia may be slight or absent early in the disease or throughout the illness in seriously ill patients.

Intradermal tests using the Bachman antigen in a dilution of 1:8000 were performed on 13 cases, with positive results in 7 cases. In the 12 cases with clinical symptoms, all those with positive tests had been ill 16 to 22 days, while those with negative tests had been ill 16 days or less.

The precipitin test was done on 11 cases and was positive in 10 instances. In the patients with clinical symptoms, positive tests were obtained on the 10th to 22d days of illness, while the only negative test was obtained on the 5th day.

It has been stated [1] that intradermal tests usually become positive after the second week of the disease and the precipitin test after the fourth week.

Walker [2] and Salan and Schwartz [3] have reported cases of trichinosis with definite neurological signs but no gastrointestinal symptoms. Meyer [4] recorded a case with neurological signs and mentioned the relatively low spinal fluid leucocyte count. Most and Abeles [5] in a report of trichinosis involving the nervous system, mention the mental changes that may occur. Although both hospitalized patients complained of headache and A. H. was found to have increased lymphocytes in the spinal fluid, no signs of encephalitis or mental disturbance occurred.

A biopsy was performed on the 53d day of illness of A. H., taking over 0.5 gm. of

TABLE 3.—*Symptomatology: Trichinosis*

Stages	Time of Onset After Infection	Location of Parasite	Symptoms Which May Be Exhibited	Tentative Diagnosis Sometimes Given
Enteral, or state of intestinal infestation	24-72 hr.	Larvae and adults in intestinal lumen and villi	Nausea Vomiting Diarrhea Constipation Abdominal pain	Food poisoning Typhoid fever Appendicitis Colitis Intestinal influenza
Parenteral, or stage of dissemination	After 4 or 5 days	Larvae in blood stream and muscles	Eosinophilia Irregular hyperpyrexia Edema, esp. suborbital Conjunctivitis Photophobia Myalgia Sore throat Dyspnea Cough Pleurisy Pneumonia Urticaria Rose spots Scarlatiniform rash Trismus Sweating	Arthritis Rheumatism Upper respiratory infection Laryngitis Conjunctivitis Influenza Intercostal neuritis Pleurodynia Measles Paranasal sinusitis Asthma Tetanus Diphtheria—laryngeal Periarteritis nodosa Dermatomyositis
		Larvae passing through heart	Chest pain Tachycardia Apical murmurs Dierotic pulse	Myocarditis Endocarditis
		Larvae in brain and meninges	Papilledema Severe headache Malaise Hyperpyrexia Disorientation Delirium Coma Loss of reflexes Head drop Stiff back Vomiting Prostration Paralyses	Encephalitis Meningitis Poliomyelitis

tissue from the gastrocnemius muscle. The specimen was examined by means of a press preparation by artificial digestion and by sectioning and staining. No trichinae larvae were found. This was indeed a surprising finding, in view of the severity of the illness and the lapse of 53 days allowing for encystment.

In the experience of one of us (F. J. B.), the gastrocnemius muscle of laboratory animals is one of the less affected muscles but nonetheless generally has about one-fourth as many trichinae per gram as the extraocular muscles or diaphragm. The number of larvae per gram necessary to produce symptoms is not known. It was once surmised that about 100 larvae per gram in the diaphragm would cause symptoms and about 1000 would be fatal. However, in two of five cases reported by Wright, Kerr, and Jacobs,[6] having between 501 and 1000 larvae, questioning of relatives revealed no history suggestive of clinical trichinosis. On the other hand, two fatal cases are reported, both with superimposed infections, one having a total infection of less than 100 larvae per gram and the other between 501 and 1000 larvae per gram.

Trichinosis may give rise to protean manifestations. Table 3 summarizes the varied symptomatology and differential diagnosis which may be encountered and considered by the physician when faced with a diagnostic problem of this nature.

The hospitalized cases described in this outbreak were treated symptomatically. According to recent reports † cortisone and corticotropin (ACTH) are effective in relieving symptoms during the acute stage.

The garbage-fed hog is the chief source of outbreaks such as the one reported here. Such epidemics can be prevented by thoroughly cooking garbage before it is fed to swine.

SUMMARY

Fourteen cases of trichinosis occurring in four households are reported. The source of the outbreak was ingested pork sausage from garbage-fed hogs. Two patients were hospitalized. Four cases were very mild and two were asymptomatic. The report of the intradermal and precipitin tests are stated. Nausea and vomiting were conspicuously absent in these cases, fever and weakness being the outstanding complaints. Eosinophilia was present in all of the 14 cases.

The cases in this epidemic demonstrated many of the protean manifestations of this disease and reflected the perplexing nature of the differential diagnosis. The consumption of pork products from hogs fed uncooked garbage represents the chief source of epidemics of this type. Prevention can be accomplished by thoroughly cooking raw garbage before it is fed to swine. As a safeguard against infection in the human, all pork products should be thoroughly cooked.

Dr. T. L. Perrin, of the National Institutes of Health, Division of Pathology, examined the biopsy material. Dr. J. Bozicevich, National Institutes of Health, prepared the antigen for the intradermal test. Dr. W. H. Wright, of the National Institutes of Health, gave many helpful suggestions.

REFERENCES

1. Augustine, D. L.: Medical Progress: Trichinosis and Enterobiasis; Their Importance in New England, New England J. Med. **226**:488, 1942.

2. Walker, A. T.: Trichiniasis: Report of Outbreak Caused by Eating Trichinosis Bear Meat in Form of "Jerky," J. A. M. A. **98**:2051, 1932.

3. Salan, J., and Schwartz, B.: Trichinosis with Involvement of the Central Nervous System, J. A. M. A. **90**:611, 1928.

4. Meyer, J.: Trichinosis, J. A. M. A. **70**:588, 1918.

5. Most, H., and Abeles, M. M.: Trichiniasis Involving the Nervous System: Clinical and Neuropathologic Review, with Report of 2 Cases, Arch. Neurol. & Psychiat. **37**:589, 1937.

6. Wright, W. H.; Kerr, K. B., and Jacobs, L.: Studies on Trichinosis: Summary of Findings of Trichinella Spiralis in Random Sampling and Other Samplings of Population of United States, Pub. Health Rep. **58**:1293, 1943.

7. Rosen, E.: Cortisone Treatment of Trichinosis, Am. J. M. Sc. **223**:16, 1952.

8. Solomon, C., and Seligman, B.: Response of Trichiniasis to Adrenocorticotropic Hormone (ACTH) Therapy, New York J. Med. **52**:1444, 1952.

† References 7 and 8.

NITROFURANTOIN THERAPY OF URINARY TRACT INFECTIONS IN CHILDREN

S. HARRIS JOHNSON III, M.D.
and
MATTHEW MARSHALL Jr., M.D., Pittsburgh

FURADANTIN, a brand of nitrofurantoin N. N. R., has been demonstrated to be an effective urinary antibacterial agent in adults * and we have found it to be equally efficacious in children, as shown in the following study.

Thirty-eight children hospitalized at either Children's Hospital or Western Pennsylvania Hospital were given nitrofurantoin for urinary tract infections. Nine of these patients were not under observation sufficiently long to evaluate the results. Nitrofurantoin was administered during 33 episodes of urinary tract infections in 29 patients, and the results of this treatment are summarized in Tables 1 and 2. Nitrofurantoin in both the liquid (Furadantin Pediatric Suspension) and tablet forms was utilized. Children who could ingest them preferred the tablets. The liquid was thought unpalatable by some, but none were intolerant of it. The liquid caused a sensation of gastric irritation in two children, but this subsided when the dosage was reduced to 6 mg. of nitrofurantoin per kilogram per 24 hours. One older child developed mild nausea while taking the tablet form. One child developed a generalized urticaria and angioneurotic edema after five weeks of therapy. None of the children developed a blood dyscrasia during or following nitrofurantoin therapy.

The patients have been divided into those who have and those who do not have an anatomic abnormality of their urinary tract. This classification demonstrates well the important role of obstruction in hindering sterilization of the urinary tract. Two-thirds of the patients without anatomic abnormality had good results. We feel that this is a high proportion of good results, since all but one of these patients had either chronic or recurrent infection in spite of previous therapy with other drugs. Approximately one-half of the patients with Proteus vulgaris infections were cured, and in this respect nitrofurantoin has been much more effective than any other drug we have used previously. We feel that this is especially important, since P. vulgaris infections occur rather commonly in infants and children.

As might be expected, the results of treatment of urinary tract infections in the presence of obstruction were not so satisfactory as among those cases in which no anatomic abnormality was present. The one good result was obtained in a patient in whom the degree of obstruction was minimal. On several occasions, nitrofurantoin has controlled acute exacerbations of fever and for that reason is of value in such cases.

Initially, we used the drug for only short periods of time and at a dosage that did not exceed 7 mg. per kilogram over 24 hours, in four divided doses. Later, we increased the dose to 10 mg. per kilogram over 24 hours and continued treatment for a period of several weeks. We found that prolonging therapy greatly increased its effectiveness. Since appreciable blood levels are not achieved with nitrofurantoin and since, therefore, this drug probably exerts its action mainly in the urinary collecting system, we feel that a longer period of therapy should be used than when an antibacterial agent with high blood levels and presumably more effect on the renal parenchyma is employed.

From the Children's Hospital and the Western Pennsylvania Hospital.

Furadantin used in this study was furnished by Eaton Laboratories, Inc., Norwich, N. Y.

* References 1-7.

TABLE 1.—*Group 1.—Results of Therapy with Nitrofurantoin in Urinary Tract Infections without Anatomic Abnormality*

Case No.	Diagnosis	Organism Before Therapy	Organism After Therapy	Comment
		A.—Good Results		
1	Chronic pyelonephritis	Proteus	None	
2	Chronic cystitis	E. coli	None	
3	Recurrent cystitis	E. coli	None	Recurrence
	Recurrent cystitis	E. coli	None	
4	Chronic pyelonephritis	Pseudomonas & Proteus	None	
5	Chronic pyelonephritis	E. coli & Streptococcus	None	
6	Chronic cystitis	E. coli	None	Recurrence
	Chronic cystitis	E. coli	None	
7	Chronic pyelonephritis	Proteus	None	Recurrence
	Chronic pyelonephritis	E. coli	None	
8	Hemorrhagic cystitis	E. coli	None	
9	Chronic pyelonephritis	Proteus	None	
10	Chronic pyelonephritis	Proteus	None	Recurrence
	Chronic pyelonephritis	Proteus	None	
11	Chronic pyelonephritis	E. coli	None	
		B.—Fair Results		
1	Chronic pyelonephritis	Proteus	Proteus	Controlled fever & symptoms
2	Chronic pyelonephritis	Proteus	Proteus	Controlled symptoms & eliminated pyuria
		C.—Poor Results		
1	Chronic pyelonephritis	E. coli & yeast	Yeast	Progressed to cortical abscesses
2	Chronic pyelonephritis	Proteus & E. coli	Proteus	Asymptomatic
3	Chronic cystitis	E. coli	E. coli	
4	Chronic cystitis	E. coli	E. coli	
5	Chronic pyelonephritis	Proteus	Proteus	

TABLE 2.—*Group 2.—Results of Therapy with Nitrofurantoin in Urinary Tract Infections with Anatomic Abnormality*

Case No.	Diagnosis	Organism Before Therapy	Organism After Therapy	Comment
		A.—Good Results		
1	Chronic pyelonephritis & persistent calyceectasis following pyeloplasty	Pseudomonas	None	
		B.—Fair Results		
1	Neurogenic bladder & unilateral hydronephrosis	Paracolobactrum	Alcaligenes	Pyuria reduced
2	Unilateral hydronephrosis & hydroureter	Micrococcus & enterococcus & E. coli	Proteus	Pyuria controlled
3	Neurogenic bladder & bilateral hydronephrosis	Pseudomonas	E. coli	Fever controlled
4	Neurogenic bladder & bilateral hydronephrosis	Micrococcus & Proteus	E. coli & Streptococcus	Fever controlled
5	Bilateral hydronephrosis	E. coli	Proteus	Pyuria controlled
		C.—Poor Results		
1	Neurogenic bladder & unilateral hydronephrosis	Pseudomonas	Proteus	
2	Ureterosigmoidostomy & colostomy	S. faecalis & E. coli	S. faecalis & Proteus & Micrococcus	
3	Postresection cystitis	Proteus	Proteus	
4	Congenital hydronephrosis	E. coli	E. coli	
5	Congenital hydronephrosis	Proteus & E. coli	Proteus	

CONCLUSIONS

1. Nitrofurantoin N. N. R. (Furadantin) is an effective urinary antibacterial agent in children.

2. The urine of over one-half of the patients with Proteus vulgaris infection was sterilized.

3. Nitrofurantoin is relatively nontoxic. The liquid pediatric dosage form is palatable.

509 Peoples E. E. Bldg.

REFERENCES

1. Abrams, M., and Prophete, B.: Furadantin: Use in the Treatment of Urinary Tract Infections, Missouri Med. **51**:280 (April) 1954.

2. Carroll, G.: Treatment of Urinary Infections: Choice of Drug, Texas J. Med. **49**:761 (Oct.) 1953.

3. Carroll, G.; Brennan, R. V., and Allen, H.: Treatment of Urinary Infections: The Choice of Drug, Chicago M. Soc. Bull. **56**:626 (Feb. 13) 1954.

4. Friedgood, C. E., and Ripstein, C. B.: Furadantin in the Treatment of Infection due to Antibiotic Resistant Organisms, Internat. Rec. Med. **167**:218 (April) 1954.

5. Mintzer, S.; Kadison, E. R.; Shlaes, W. H., and Felsenfeld, O.: Treatment of Urinary Tract Infections with a New Antibacterial Nitrofuran, Antibiotics & Chemother. **3**:151 (Feb.) 1953.

6. Norfleet, C. M., Jr.; Beamer, P. R., and Carpenter, H. M.: Furadantin in Infections of the Genito-urinary Tract, Trans. Southeast. Sect. Am. Urol. A., April 3, 1952, p. 26.

7. Schatten, W. E., and Persky, L.: Furadantin in the Therapy of Genitourinary Tract Infections, Am. J. Surg. **86**:720 (Dec.) 1953.

TEN-DAY TREATMENT OF PINWORM INFECTION WITH PIPERAZINE

LIEUT. VIRGIL M. HOWIE (MC), U.S.A.F.

THE SUCCESSFUL treatment of enterobiasis with piperazine has been reported by Mouriquand and co-workers,[1] Turpin and co-workers,[2] White and Standen,[3] and Bumbalo and co-workers.[4] White and Bumbalo treated their patients for seven days, rested for seven days, and then treated for seven more days. This clinical study was instituted to determine the effectiveness of piperazine over a 10-day period of treatment. It was hoped that this would simplify the treatment schedule and prove economical to the parents.

All patients included in this study were treated by me in the Langley Air Force Base Dependent Clinic. All diagnostic and post-treatment Cellophane (Scotch) tape swabs were examined in the 4450th USAF Hospital laboratory. Cellophane-tape swabs of the anal area were obtained in the early morning by the parents when clinical or parental suspicion of pinworm infection was present. All siblings and some parents of children found to be infected with pinworms were also examined by the same method. Usually no more than three pretreatment swabs were taken to establish the diagnosis. Routine Cellophane-tape swabbing of all clinic patients was not performed.

All patients with one or more positive Cellophane-tape swabs were treated with piperazine hexahydrate in the form of a liquid suspension containing 100 mg. per cubic centimeter (Syrup of Antepar, Burroughs Wellcome & Company, Inc.). Dosage varied from 56 to 133 mg. per kilogram daily, with an 83 mg. mean daily dose. Ninety-three per cent of doses were in the range of 66 to 100 mg. per kilogram daily. The drug was given in two or three equal doses for a period of 10 consecutive days. Families were treated as a group, with all infested patients and most of the other children in the household being treated at the same time. No personal or environmental hygienic measures were suggested to the parents.

Cellophane-tape swabbing of the anal area for seven consecutive days was started approximately two weeks after completion of the 10-day treatment period. The criteria for cure were seven negative post-treatment Cellophane-tape swabs. One or more positive post-treatment swabs was considered a treatment failure. Some treatment failures were retreated with an increased dose of piperazine.

The patients' ages ranged from 11 months to 33 years. There were 28 patients in the 1- to 5-year age group; 20 patients in the 5- to 10-year age group, and 10 patients 10 years of age or older, with 6 of these being women. Twenty-three other patients were treated but were not included in the statistics of this study owing to lack of laboratory proof of diagnosis or inadequate follow-up. There were 37 families treated in this study.

Some toxic effects possibly due to the drug were noted in this study in contrast to the lack of toxic effects noted in earlier studies. A 27-month-old infant was reported by the mother to have started vomiting intermittently on the fifth day of treatment, and the vomiting stopped on the seventh day, when the piperazine was discontinued. This infant was taking 79 mg. per kilogram daily (1 teaspoon b. i. d.). The 25-year-old mother of this patient, who was taking 73 mg. per kilogram daily (4 teaspoons b. i. d.) reported that she was "dizzy," dropped objects, and had difficulty with her memory from the second to the seventh day of treatment, when she discontinued the piperazine. Unfortunately, neither of these patients was examined by a physician while symptomatic, and these symptoms were reported several days later.

A 27-year-old mother who was being retreated with a dose of 91 mg. per kilogram daily (5 teaspoons b. i. d.) was seen by another physician because of vertigo. The patient had previously had chronic sinusitis, and he attributed her vertigo to a labyrinthitis and treated her by discontinuing the piperazine and giving her an antihistaminic drug. Her symptoms disappeared rapidly.

An 8-year-old patient, being retreated with a dose of 104 mg. per kilogram daily (2½ teaspoons b. i. d.), complained of not being able to read his book in school on the fifth day of retreatment. This symptom disappeared the next day, when treatment was discontinued. His 6-year-old sister, who was being retreated on a dosage of 133 mg. per kilogram daily (2 teaspoons b. i. d.), began to have severe vertigo on the fifth day of retreatment and was seen by a physician that night. The physician reported that she had severe vertigo and fell from side to side when seated. These symptoms and signs disappeared the next day after treatment was discontinued.

Two out of the five patients reported above with unusual symptoms while taking the piperazine had vertigo, as determined objectively by an examining physician. The three others had symptoms suggestive of vertigo. All of the symptoms disappeared after discontinuation of the piperazine. Three of the five were being retreated with larger than average doses of piperazine due to the failure of the initial 10 days of treatment. The patient with the most severe symptoms was on the largest dosage schedule used in this study. If these symptoms were due to drug toxicity, then White and Standen's report [3] that the drug was well tolerated up to a dosage of 150 mg. per kilogram daily was not confirmed by this study.

There were 9 treatment failures out of 58 patients treated for pinworms, giving a cure rate of 84%. Two patients who had negative pretreatment swabs had positive posttreatment swabs and were considered treatment failures. Two of the nine treatment failures were cured by five more days of piperazine therapy. The nine treatment failures were found in all age groups. This study confirms the earlier studies in that piperazine hexahydrate is an effective oxyuricide.

SUMMARY

Fifty-eight patients with pinworms were treated with piperazine hexahydrate with dosages ranging from 56 to 133 mg. per kilogram daily for 10 consecutive days, with an 84% cure rate.

Five patients showed possibly toxic symptoms while taking piperazine hexahydrate, and these symptoms disappeared with discontinuation of the drug.

4450th U. S. A. F. Hospital, Langley Air Force Base, Va.

REFERENCES

1. Mouriquand, G.; Roman, E., and Coisnard, J.: Essai de traitement de l'oxyurose par la pipérazine, J. méd. Lyon **32**:189 (March 5) 1951.

2. Turpin, R.; Cavier, R., and Savaton-Pillet, J.: Traitement de l'oxyurose par le di (phénylacétate) de pipérazine (D. P. P.), Thérapie **7**:108, 1952.

3. White, R. H. R., and Standen, O. D.: Piperazine in the Treatment of Threadworms in Children: Report on a Clinical Trial, Brit. M. J. **2**:755 (Oct. 3) 1953.

4. Bumbalo, T. S.; Gustina, F. J., and Oleksiak, R. E.: The Treatment of Pinworm Infection (Enterobiasis): A Comparative Study of 3 Oxyuricides, J. Pediat. **44**:386 (April) 1954.

NEONATAL BLOOD PRESSURE STUDIES

ABRAHAM I. SCHAFFER, M.D., New York

THE INDIRECT determination of the blood pressure in the newborn infant is the chief subject of this report. The methods discussed include ausculation, palpation, the flush method, and, finally and most important, a method using impedance plethysmography. The problem of the proper width of the cuff is analyzed in detail. Also noted are observations on the range and variation of the normal neonatal systolic pressure.

My interest in this subject arose from a desire to explain why an occasional normal newborn infant shows a pattern of left ventricular preponderance in both the electrocardiogram and vectocardiogram.[1] Usually the neonatal record shows such a degree of right preponderance that one cannot diagnose an abnormal degree of right preponderance from a single tracing in the early weeks of life. Serial tracings during the first three months are necessary. Normally they show a decreasing degree of right preponderance; only if the degree appears to increase is one justified in diagnosing abnormal right preponderance.* The occasional appearance of left preponderance in normal infants might be caused by hypertension. Therefore, an attempt was made to measure their blood pressure. This proved to be a difficult problem and resulted in the work here reported.

The clinical usefulness of neonatal pressure determinations is at present restricted to the problem of diagnosing coarctation. Should it become practical as a routine procedure, other uses may be found.

Aided by a grant from the Research Fund of the New York Medical College.

From the Departments of Medicine and Pediatrics, New York Medical College, Metropolitan Hospital Division.

* References 2 and 3.

METHODS

Impedance plethysmography was used to register the pulsations that reached the limb distal to the occlusive cuff.† A high-frequency alternating current is sent through a segment of the forearm. As the volume of the forearm changes with each pulse, the impedance of the segment varies proportionately. The impedance changes are detected by a bridge circuit and recorded by an electrocardiograph. The record has the value of a plethysmographic pulse, which has been shown to be identical with the pulse registered by the more conventional air or water plethysmographs. The advantage of the impedance method is the increased sensitivity, which permits an accurate registration of the small neonatal pulse.

The cuff pressure was measured by an electric manometer (Sanborn Electromanometer), which was connected to one channel of a two-channel direct writer (Sanborn Twin-Viso Electrocardiograph). The second channel recorded the plethysmographic pulse. The manometer was accurately calibrated; there was no need to calibrate the plethysmograph as long as its sensitivity was adequate to register the pulse clearly.

When the cuff pressure is raised to suprasystolic levels, the plethysmographic pulse disappears. As the presure is lowered slowly, there comes a point where the pulse reappears. This is the systolic endpoint; it was very clear and reproducible in all cases. The determination can be recorded in its entirety by recording both the cuff pressure and the plethysmographic trace; or the determination can be made visually by watching the stylus for the plethysmographic pulse and then reading the cuff pressure on the mercury manometer. The latter procedure was somewhat less accurate than the former. Numerous determinations can be done without examiner fatigue and with no discomfort to the infant. The pressure cuff and the electrodes did not interfere with the baby's position or movements, so that once they were applied the baby usually became quiet. The various controls and switches were so arranged that their operation did not jar the baby or the crib. The actual inflation and deflation of the cuff did not stimulate the infant appreciably; even keeping the cuff inflated for several minutes did not appear to disturb him. A pressure could be recorded graphically with the plethysmograph twice a minute for several minutes and once every two

† References 4 and 5.

minutes for hours. With this method, it is possible to place all the equipment and the examiner in an adjoining room and still record systolic pressures for extended periods of time. Whereas auscultation became impossible when the infant cried, the plethysmograph could still on occasion register a systolic pressure.

Auscultation, palpation, and the flush method were the other methods used to determine the systolic pressure. Auscultation of the Korotkoff sounds was done with the aid of the Fox localizer, a special stethoscopic chest piece, which consists of a diaphragm into which is screwed a short rod. The tip of the latter was placed precisely over the brachial artery as determined by palpation.‡ The flush method is described by Goldring and Wohltmann.[6]

Three cuffs were used: 8 by 13 cm., 4 by 7 cm., and 2.5 by 4 cm. When the 8 cm. cuff was folded in half, it measured 4 by 13 cm. Since it was found to be the equivalent of the 4 by 7 cm. cuff, no distinction will be made between the folded 8 cm. and the 4 cm. cuffs. Both will be designated as the 4 cm. cuff.

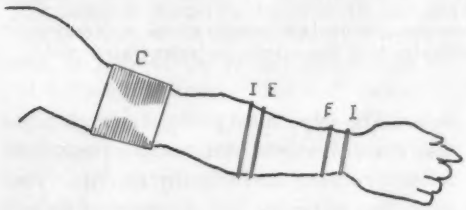


Fig. 1.—Arrangement of cuff (*C*) and electrodes (*I,I* and *E,E*). *I,I* are the electrodes which introduce the high-frequency alternating current; *E,E* are the electrodes which measure the impedance of the segment of the arm which lies between them. The electrodes consist of a folded strip of aluminum foil 4 to 6 mm. wide. The cuff is connected to a manometer, the electrodes to the impedance plethysmograph, and these to a two-channel recorder.

RESULTS

For the purposes of this report, plethysmography and the 4 cm. cuff will be used as the standard method for the indirect determination of the systolic pressure. Its absolute accuracy is not known, since no intra-arterial pressures were taken for controls. The plethysmographic detection of the pulse proved to be very sensitive and reliable. The cuff, especially its width, was the factor limiting the accuracy of the method. Because the 4 cm. cuff was convenient and gave reasonable readings, it was used as the standard. Further work may very well indicate that some other width is the best for the newborn infant.

In about three-fourths of the cases where auscultation was also used, at least one reading was successful. Whenever the sounds could be heard with confidence, the results agreed very closely with the plethysmographic method. On the other hand, the flush and palpatory methods were erratic and unreliable.

The systolic pressure measured in the arm with the 4 cm. cuff ranged from 52 to 102 mm. Hg in the 24 infants examined during the first day of life. The examination was done at a time when the infants tended to be quiet; that is, either before they were old enough to manifest hunger or after a feeding. They were examined while lying supine or on the side. Some slept during the procedure, and some sucked a bottle of water or a dry nipple to keep them quiet.

A session lasted usually 30 to 90 minutes, during which time some 5 to 25 pressure determinations were done with the various methods. During the course of a session, the pressure varied usually by 10 to 20 mm. Hg; several infants showed a variation of 20 and one of 27 mm. Hg. These fluctuations did not appear to be related to changes in the infant's behavior. It was occasionally possible, as the cuff pressure was lowered very slowly, to register the phase where only some of the pulses came through the cuff. This indicated the range of the respiratory variation of the systolic pressure (Fig. 2).

The 2.5 cm. cuff invariably gave readings higher than the 4 cm. cuff. The difference ranged from 20 to 170 mm. Hg. When the narrow cuff, which was also short, was adjusted so that the bag lay directly over the brachial artery, the recorded pressure was lowest and usually was about 20 to 50 mm. Hg above the pressure obtained with the 4 cm. cuff. If the 2.5 cm. cuff was improperly placed, the difference was much more, usually about 50 to 70 and in one instance 170 mm. Hg. Changing the application of the 4 cm.

‡ Dr. Dorothy Yang of the Department of Pediatrics, showed me how to dectect the Korotkoff sounds with the Fox localizer.

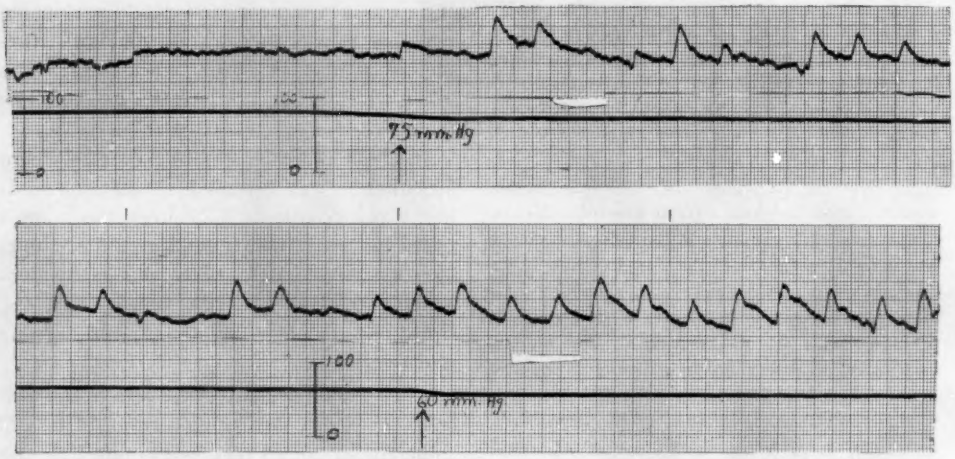


Fig. 2.—An example of the determination of the systolic pressure with the impedance plethysmograph. Each strip contains two channels; the lower strip is a continuation of the upper. The upper channel shows the plethysmographic pulse; the lower channel shows the cuff pressure. Time lines are 0.04 and 0.2 seconds. At the first arrow where the cuff pressure is 75 mm. Hg, the first pulse is noted. At the second arrow, 60 mm. Hg, all the pulses are registered. Between the two pressures, some of the pulses do not pass through the cuff because of the respiratory variation of the blood pressure. This record indicates that the systolic pressure varies with respiration between 75 and 60 mm. Hg.

cuff had little effect on the readings unless it had been applied loosely; making it more snug decreased the recorded pressure somewhat. In one instance the pressure decreased 18 mm. Hg.

COMMENT

There are many reports § claiming that oscillometry can indicate both the systolic and the diastolic pressure. Basically, oscillometry is the registration of the plethysmographic pulse of the limb segment which lies either underneath or distal to the cuff. With the impedance plethysmograph, this pulse could be accurately registered for the first time in the newborn infant. Accordingly it was hoped at the start of this investigation that the measurement of the diastolic as well as the systolic pressure would be possible.

The diastolic level is supposed to be indicated by any or several of the following characteristics of the pulse curve which develop as the cuff pressure is lowered: a sudden decrease in the amplitude, a steep ascent of the upstroke, a sharp angle made by the end of the diastolic segment with the upstroke, and a large negative presystolic wave. The impedance plethysmograph registers the pulse very well, and all these characteristics were noted in my records. However, they appeared and disappeared in such a way that it was impossible to correlate them with the probable diastolic pressures. Any attempt to deduce the diastolic pressure from them gave impossible results.

A reexamination of the literature makes it appear likely that the pulse form is the resultant of many factors besides the filling state of the artery, which is supposed to be the crucial determinant. There are unpredictable changes in the reflected waves, the elasticity and vibrational qualities of the arterial wall, the filling state of the tissues, and even the characteristics of the recording device. While it is possible to correlate a pulse form with the diastolic pressure in a given person at a given time, yet if the conditions change even slightly the correlation becomes invalid.

Impedance plethysmography, like other oscillometric methods, can record the pulse of the segment of the limb lying either underneath or distal to the cuff, depending on the position of the electrodes. When they lie underneath the cuff, the systolic end-point is obscured by suprasystolic pulsations. These

§ References 8, 9, and 10.

are pulses that appear at cuff pressures much higher than systolic. They have penetrated through the upper edge of the cuff (where the effective pressure on the artery is much less than the cuff pressure) and have produced a volume change underneath the uppermost electrode. A few determinations with the electrodes underneath the cuff showed the disturbing nature of the suprasystolic pulsations. Thereafter all measurements were made with the electrodes distal to the cuff; this always gave a clear and reliable systolic end-point.

In the lower extremity systolic pressures can be readily determined by placing the cuff on the thigh and the plethysmographic electrodes on the leg. Because the cuff is easily soiled with feces, this method was not used often. The neonatal thigh being larger than the arm, it requires a wider cuff. However, at present the proper dimensions are not known. Because of the cuff factor the accuracy of all indirect methods, whether on the upper or lower extremities, is uncertain; accordingly any comparison between arm and thigh pressures should take this into consideration.

Ausculation proved to be just as accurate though not as reliable as the plethysmograph for the determination of the systolic pressure. Whenever I could observe the Korotkoff sounds and the plethysmographic pulse together, they appeared almost simultaneously. As the cuff pressure was lowered, one or the other might appear a few millimeters of Hg earlier, but the difference was never significant.

The sounds were best heard at the systolic level. Occasionally they could be heard for a range of 20 to 30 mm. Hg, usually they disappeared earlier so that no diastolic pressure could be estimated. Dr. Yang, in a personal communication, states that she can ascertain the diastolic pressure in many newborn infants. Possibly audioamplification might correct for a lack of acute hearing of some observers.

I was able to determine the systolic pressure by auscultation at least once in about three-fourths of the infants examined thus. After the age of one month, both systolic and diastolic Korotkoff sounds can be heard routinely. It should be noted that auscultation suffers from the same inaccuracies as all other indirect methods employing a cuff. Auscultation is just as accurate as the plethysmograph for systolic pressures, and it requires no elaborate instrumentation. However, it fails frequently because of examiner fatigue, room noise, and deviation of the tip of the stethoscope from the brachial artery. Examiner fatigue, especially, interferes with repeated determinations.

Palpation of the brachial or radial artery usually gave readings about 10 to 30 mm. Hg below the plethysmographic method. It was often impossible to be confident of the presence or absence of a pulse.

The flush method is simple but coarse and unreliable. The results varied considerably with the rate of lowering of the cuff pressure and the ability to recognize a slight flush. Neither palpation nor the flush method appear to be suitable as a clinical method.

The accuracy of all indirect methods is limited seriously by the imperfections inherent in the occlusive cuff.|| It is well established that the readings obtained depend greatly on the width, length, and fit of the cuff. The wider the cuff the lower the reading; the shorter the cuff the more variable the reading; and finally, the looser the cuff the higher the reading. The mechanisms responsible for this involve, first, the efficiency of the transmission of the pressure in the cuff to the artery and, second, the resistance which the cuff offers to the pulse traveling underneath it.

The efficiency of pressure transmission varies directly with the width of the cuff. When the cuff is narrow, a large proportion of its pressure is wasted in compressing and displacing the soft tissues. Therefore the pressure exerted on the artery, which is the ultimate consideration, is much less than that in the cuff. The wider the cuff the less percentage of pressure is wasted and the

|| References 7, 8, 11, and 12.

more accurately does the cuff pressure approximate the pressure exerted on the artery.

Opposing the above mechanism is the second factor which involves the resistance offered by the width of the cuff to the passage of the pulse through it. As the pulse traverses the compressed segment of the artery, it suffers a decrement because of friction. The wider the compressed segment (that is, the wider the cuff), the more loss of energy and the greater the tendency for the pulse to be lost before it reaches the lower border of the cuff. This means that the cuff must decrease its pressure on the artery to allow a larger portion of pulse to enter the compressed segment, a portion sufficient to overcome the resistance and become perceptible distal to the cuff. Accordingly, here also the relationship holds that the wider the cuff the lower the recorded blood pressure.

This relationship is quantitatively dependent to some extent on the shape of the pulse wave. The part of the pulse which lies near the top represents the energy available for overcoming the cuff resistance when the artery is being compressed by near systolic pressures. If this segment of the pulse curve is flat, there will be more energy available than when it is peaked. According to the illustrations in Woodbury's report,[7] the normal neonatal pulse is flat on top, while the premature infant's pulse is peaked. This suggests that in the premature infant the resistance factor is more important than in the full-term infant.

A wide cuff increases the resistance factor, while a narrow cuff increases the loss of pressure transmission. For any given case there will be a width where the two actions neutralize each other, resulting in an accurate pressure reading. This critical width will vary to some degree from person to person. However, by using direct intra-arterial pressures as a control, it is possible to find a width most accurate for a given class of patients.

The inflatable bag of the cuff should be long enough to encircle the limb completely.[11] If it is not, the bag must be placed directly over the artery to insure the maximum efficiency of pressure transmission. The infant arm has a circumference of 7 to 10 cm. The 2.5 by 4 cm. cuff is too short for this. I have found it difficult to place this cuff properly at the first try, and have noted differences of 20 to 40 mm. Hg in the systolic readings for diffrent positions of the bag. Even with the longer cuffs the placement must be done carefully so that it is snug. I have noted on one occasion a decrease of 18 mm. Hg after the cuff was made more snug. Some of the variation of the pressure during an experimental session could have been caused by changes of the snugness of the fit of the cuff.

Woodbury, Robinow, Hamilton, and Volpitto¶ recommended the 2.5 cm. wide cuff for the indirect measurement of the systolic pressure in the newborn infant. They based it on the comparison of the direct intra-arterial pressure readings with those obtained by palpation. They were fully aware of the influence that the width of the cuff has on the pressure readings. The American Heart Association [11] recommends the 2.5 cm. width and does not specify any length except that in a general statement it indicates the desirability of a bag that is long enough to encircle the arm.

If palpation plus a 2.5 cm. wide cuff gives accurate systolic pressure readings, then a more sensitive pulse detector, such as the plethysmograph or auscultation, will give too high readings with a 2.5 cm. cuff. I have not compared my results with intra-arterial recordings, so that a definitive recommendation is not possible, but the readings obtained with the 4 cm. cuff seem reasonable. At present I would suggest that a 4 cm. cuff be used, one long enough to encircle the arm completely. A suitable cuff, commercially available, is 8 cm. by 13 cm. This can be folded in half and it will then act as a 4 cm. wide cuff. The so-called neonatal cuff (2.5 cm. by 4 cm.) is too short and probably too narrow. For the detection of the pulse, auscultation, impedance plethysmography, or some other sensitive method would be better than either palpation or the flush method.

¶ References 7 and 12.

CONCLUSIONS

1. The impedance plethysmograph is an excellent instrument to detect pulsations in the newborn infant for the purpose of determining the systolic blood pressure. Auscultation is just as accurate but not as reliable because of the frequent failure to hear the sounds. 2. Diastolic pressures could not be obtained with either method. 3. The flush method and palpation were found to be unsatisfactory. 4. All indirect methods employing an occlusive cuff suffered from large errors inherent in all cuffs. The width is the chief critical factor. The officially recommended neonatal cuff as is now commercially available (2.5 by 4 cm.) is definitely too short and probably too narrow when used with a sensitive pulse detector. The correct size is not yet known.

Dr. Jan Nyboer and Dr. Sam Gelfand gave advice in this study. Mr. Sam Bagno designed the circuit of the impedance plethysmograph used in this investigation and helped in its miantenance. Dr. Lawrence Slobody was interested in this project, and Misses Josh and Riley, nurses in the Newborn Nursery of Metropolitan Hospital, cooperated in this work.

REFERENCES

1. Schaffer, A. I., and Beinfield, W. H.: The Vectorcardiogram of the Newborn Infant, Am. Heart J. **44**:89, 1952.

2. Schaffer, A. I.; Burstein, J.; Mascia, A. V.; Barenberg, L., and Stillman, N.: The Unipolar Electrocardiogram of the Newborn Infant, Am. Heart J. **39**:588, 1950.

3. Schaffer, A. I.: Unipolar Electrocardiographic Studies in Congenital Heart Disease in Infancy, Am. J. Dis. Child. **80**:260, 1950.

4. Nyboer, J.: Electrical Impedance Plethysmography: Physical and Physiologic Approach to Peripheral Vascular Study, Circulation **2**:811, 1950.

5. Nyboer, J.: Plethysmograph: Impedance, in Medical Physics, edited by O. Glasser, Chicago, Year Book Publishers, Inc., 1950, Vol. 2, p. 736.

6. Goldring, D., and Wohltmann, H.: Flush Method for Blood Pressure Determinations in Newborn Infants, J. Pediat. **40**:285, 1952.

7. Woodbury, R. A.; Robinow, M., and Hamilton, W. F.: Blood Pressure Studies on Infants, Am. J. Physiol. **122**:472, 1938.

8. von Bonsdorff, B.: Zur Methodik der Blutdruckmessung, mit besonderer Berücksichtigung der Registrierung absoluter Sphygmogramme beim Menschen, Acta med. scandinav. Supp. 51, p. 1, 1932.

9. Bazett, H. C., and Laplace, L. B.: Studies on the Indirect Measurement of Blood Pressure: Sources of Error in Riva Rocci Method, Am. J. Physiol. **103**:48, 1933.

10. von Recklinghausen, H.: Neue Wege der Blutdruckmessung: Fünf Abhandlungen über Blutdruck und Puls in den grossen Arterien des Menschen; Theorie der unblutigen Blutdruckmessung auf Grundlage der Treppenkurve, Ztschr. klin. Med. **113**:1, 1930.

11. Bordley, J., III; Connor, C. A. R.; Hamilton, W. F.; Kerr, W. J., and Wiggers, C. J.: Recommendations for Human Blood Pressure Determinations by Sphygmomanometers, Circulation **4**:503, 1951.

12. Robinow, M.; Hamilton, W. F.; Woodbury, R. A., and Volpitto, P. P.: Accuracy of Clinical Determinations of Blood Pressure in Children, with Values Under Normal and Abnormal Conditions, Am. J. Dis. Child. **58**:102, 1939.

INHALANT ALLERGENS IN MANAGEMENT OF ATOPIC DERMATITIS

LOUIS TUFT, M.D., Philadelphia

ATOPIC dermatitis, or allergic eczema, can be and often is a troublesome affliction of children, especially in infancy and early childhood. For many years, especially in the early part of the century, it was considered strictly a local dermatologic problem being treated like other "eczemas." In the absence of more definite etiologies, neurogenic or psychogenic factors often were considered of primary importance—which explains the designation "neurodermatitis" given to it in 1902, by Brocq. Its frequent association with asthma and hay fever was noted as early as 1892, by Besnier, who was the first to describe the disease as an independent form of prurigo—hence the designation "Besnier's prurigo." However, its relationship to allergy was not definitely established until much later. Beginning in 1932, chiefly through the efforts first of Sulzberger and Coca and later of Hill and others, the allergic etiology was clearly established, based upon the following evidence: its frequent association or alternation with asthma or hay fever, the high incidence of a family history of allergy, the frequent associated eosinophilia, the frequent occurrence of positive skin tests to food and inhalant allergens, and the clinical demonstration of the specific etiologic relationship of some allergens, notably foods, to the dermatitis. These features prompted Sulzberger and Coca [1] to designate this condition as atopic dermatitis to indicate an inflammatory condition of the skin appearing in a person predisposed by virtue of heredity to develop specific sensitization. According to these criteria, then, atopic dermatitis may be described as an acute, subacute, or, more often, chronic inflammatory disease of the skin involving especially the flexures and characterized by intense itching, papulation, thickening, and lichenification of the involved areas. It is associated with specific sensitizations to "protein allergens" responsible for the development of characteristic forms of the clinical disease in an atopic dermatitis patient.

Following these reports, other demonstrations of the allergic nature of this condition were offered, especially as it affects children. Thus, Hill and Sulzberger, in 1935, were able to delineate three stages of the disease: the first affecting infants up to 1 or 2 years of age, the second affecting older children, between 2 years and puberty, and the third affecting adults. These three phases at times were separated by intervals of a year or more, or they would continue uninterruptedly, or in some instances one or two phases were missing. Of the three, the second and third stages closely resembled one another and in fact frequently merged or passed from one to the other. In addition to this description of the nature and clinical character of the disease, Hill [2] also was able to establish the etiologic importance of food allergy, especially in infants and young children, as determined by skin tests or clinical trial or both. These observations were confirmed by many other reports and by the clinical experiences of other allergists and pediatricians. They found that removal of allergenic foods, especially egg, from the diets of these children was followed by improvement in the dermatitis, whereas reintroduction caused exacerbation. Although egg, milk, and wheat were considered to be the most important offenders, other foods—in fact any food—could be responsible.

But despite this apparently convincing evidence of the importance of food allergy,

Read in part and by proxy before the Argentine Allergy Society Sept. 10, 1953.

Chief of the Clinic of Allergy and Applied Immunology, Temple University Hospital, and Associate Professor of Medicine, Temple University School of Medicine.

further study and clinical experience demonstrated that elimination of skin-test-positive food allergens did not produce the expected beneficial results, especially in older children and adults and even in some younger children. Furthermore, wide discrepancy was noted between the positive skin reactions and the results of food withdrawal. Thus, in many instances, elimination of the positive food reactors was not followed by notable clinical improvement. As a consequence, many lost faith in these methods and again became skeptical about both the relationship of food allergy to atopic dermatitis and the value of skin tests in the diagnosis of atopic dermatitis. This has resulted in a renewed consideration of other possible etiologies, notably psychogenic or infectious causes, bringing us back to the era before 1932, when the disease was considered strictly a dermatologic problem to be treated by local applications, by nonspecific therapy, or by psychogenic means. It is of little wonder, therefore, that practitioners are discouraged about treating these patients and are relieved when they fail to return. This discouragement is shared not only by the general practitioner, the pediatrician, or the dermatologist, but until recently even by some allergists.[8] It is not surprising also that many practitioners are confused as to the etiology of this disease, the value of skin tests, and, especially, as to the clinical management of these patients.

One of the chief reasons for this confusion is the assumption that food allergens are the most important causative agents—hence, when the elimination of positive food reactors fails to relieve patients, the attending physician is led to believe not only that food allergy is not a factor but also that skin testing is of no value in diagnosis. For some unknown reason, little or no attention has been given to the importance of inhalant allergens, despite the fact that a possible relationship previously had been suggested by many writers,* even though none of the latter were entirely clear as to the manner in which the dermatitis was brought about. In order to emphasize the significance of this relationship, in 1949[9] I reported the results of a study of 54 patients with atopic dermatitis in which, upon the basis of clinical and skin test evidence, house dust, pollens (especially ragweed), and wool were shown to be outstanding inhalant offenders; also inhalants like atmospheric mold, animal danders, silk, and cooking odors were important offenders. In many patients included in that series a clinical correlation between the specific inhalant giving a positive skin reaction and the patient's outbreaks could be obtained. Thus, for example, some patients noted increased itching of the skin after dust contact. In other instances, dust-sensitive patients were relieved by environmental change either at the hospital or at the seashore. In the latter group, dust desensitization properly carried out was followed by relief. Similar clinical and skin-test evidence emphasized the etiologic relationship of other inhalant allergens.

While the results of these studies confirmed the opinion of others that inhalant allergens were important factors in atopic dermatitis, the evidence upon which it was based still was purely clinical and hence subject to questionable interpretation. However, my associates and I were able to obtain more convincing proof in subsequent experimental clinical studies, reported between 1950 and 1952. In the first of these studies[10] we were able to induce atopic dermatitis in susceptible subjects repeatedly both by inhalation of the specific offending autogenous house dust in a powdered micronized form and by injections of the specific house-dust extract. We also were able to do this by inhalation of powdered Alternaria and by injection of its extract; in addition, we presented evidence that the reaction apparently is mediated through the sweating mechanism.[11] Finally, in 1952,[12] in a similar experimental and clinical study, we were able to induce atopic dermatitis in susceptible subjects both by inhalation of ragweed pollen and by injection of its extract, thus proving convincingly that seasonal inhalant allergens, notably ragweed pollen, could be and frequently were impor-

* References 4-8.

tant etiologic factors in atopic dermatitis and deserved proper consideration in the management of this condition.

Actually, one need not be surprised that inhalants are important in atopic dermatitis, especially in older children. As already indicated, atopic dermatitis closely resembles allergic bronchial asthma; in fact, the two conditions have so many characteristics in common in relation to etiology, diagnosis, and treatment that atopic dermatitis might properly be designated "asthma of the skin." Thus both conditions frequently coexist or alternate in the same patient. Atopic dermatitis in infancy often is supplanted by asthma of childhood or later life and vice versa. As in asthma, patients with atopic dermatitis are often worse in the winter and especially at the times of seasonal change from summer to fall and winter to spring. Positive skin reactions are obtained in about the same proportion in both conditions and have about the same clinical significance. Food allergens admittedly are more important than inhalants not only in asthma of infants and young children but also in atopic dermatitis; on the other hand, inhalant allergens are more prominent than foods in asthma affecting older children or adults; yet strangely enough, the same reasoning has not been applied similarly to the counterpart of asthma in the skin; namely, atopic dermatitis.

Our previously reported investigations of patients with atopic dermatitis included both adults and children, no attempt being made to differentiate the two groups. Because foods formerly were considered the major allergenic factors in infants and young children, most reported studies, especially those of Hill, concerned themselves largely with sensitization to foods, little attention being given to inhalant allergens. In view of our recently acquired knowledge and proof of inhalant allergy, it seemed worth while to review our case records of infants and young children with atopic dermatitis to determine whether inhalant allergens are equally important in childhood. The present report contains the results of these studies as well as additional clinical data and suggestions as to treatment which from our experience might help in the management of these patients.

In all, a total of 76 patients were included. These varied in age at the time the patient first was seen from 1 to 12 years. Two were first seen in infancy, one at the age of 2 months and the second one at 9 months. Eighteen of the 76 (including the 2 infants) were 2 years old or younger and had the type designated by Hill as the infantile type; the remaining 58 had the childhood type.

It is of interest as shown in Table 1 that the onset of the dermatitis in most of the children occurred in infancy, often in the first few months of life. In very few children in whom this history was obtainable did the dermatitis begin in later childhood.

TABLE 1.—*Age of Onset in Sixty-Three Children with Atopic Dermatitis*

Age Period	No.
Birth to 6 mo.	35
6 mo. to 1 yr.	11
1 to 2 yr.	11
5 yr.	3
Up to 10 yr.	3

While some children were seen primarily because of the dermatitis, most of them came originally for a concomitant atopic condition, usually hay fever or asthma, or developed the dermatitis subsequently. Thus only 18 of the 76 children were seen primarily for the dermatitis, and of these, 11 were children less than 2 years of age with the infantile type of atopic dermatitis. Twenty-six of the group had an associated asthma, which was the primary complaint especially in the older children; 10 had seasonal hay fever, and 9 had both asthma and hay fever along with the dermatitis.

Complete allergy studies, including history, physical examination, and intracutaneous skin tests, were done in all 76 patients. Testing was done not only with extracts of those foods eaten by the patients but also with the same common inhalants (including pollens and molds) as would be employed in the routine testing of a child with asthma of unknown etiology. All positive reactions were

retested at least once to make certain of their specificity; likewise, whenever possible, an attempt was made to determine their clinical significance either by correlation with the original history or by clinical trial. This was easier to accomplish with food allergens than with inhalants; nevertheless, it was sometimes possible after the tests were done to obtain verification in retrospect of clinical sensitivity to such inhalants as house dust, animal danders, or wool. A summary of the results of the allergic studies relating to inhalant allergens is contained in Table 2.

It becomes obvious at once from inspection of Table 2 that, as in asthma, all the inhalant allergens are not equally significant as causative factors in atopic dermatitis as it affects infants and children. The exact incidence is difficult to ascertain because most of the statistical data depend upon skin-test evidence. Upon the basis of the latter as well as from clinical experience, there seems little doubt that the most important inhalant offenders in children as in adults are house dust, wool, and seasonal inhalant allergens. The latter group will vary according to the plant flora of the particular area or region in which the patient resides; thus, in our own area, representing the Northeastern United States, the most frequent offenders are ragweed pollen and Alternaria. Other inhalants, like animal danders, silk, orris root, and insecticides, play a definitely less important role. These will be considered in more detail now and in the order named, purely for convenience and not to indicate their relative incidence.

TABLE 2.—*Results of Allergic Studies in Children with Atopic Dermatitis*

Allergen *		No. of Cases Studied	Number and Degree of Reactions to Skin Tests (I. C.)				Number Clinically Sensitive	
			Negative	Slight	Moderate	Marked	By History	After Tests
House dust		76	0	13	46	17	0	6
Pollens	Ragweed	76	13	26	23	14	8	1
	Timothy	75	47	23	2	3	1	0
	Plantain	75	50	21	4	0	0	0
Molds	Alternaria	63	46	8	6	3	0	0
Animal danders	Feathers	76	25	40	11	0	0	0
	Cat	76	64	11	1	0	0	1
	Dog	76	67	9	0	0	0	1
	Horse	76	64	7	4	1	0	2
	Rabbit	74	69	5	0	0	0	0
Wool		76	28	46	1	1	6	20
Silk		70	54	12	4	0	0	0

* Routine testing strengths used for all allergens.

HOUSE DUST

Although, as in asthma, nearly all patients have a positive skin test reaction, the exact importance of house dust in atopic dermatitis in children is more difficult to ascertain than in asthma in children or adults or atopic dermatitis in adults because it depends mostly upon clinical evidence and especially upon the results of treatment directed toward dust control. Thus adults, especially housewives, often will notice increased wheezing or sneezing following exposure to house dust during dusting operations in the house. But such a history obviously is difficult to obtain in children, especially young ones, although the latter undoubtedly must be exposed frequently while crawling around the living room or bedroom on dusty rugs. Furthermore, even when an exposure of this type either induces or aggravates a dermatitis, it is much harder to determine this than in an asthmatic patient. This is because in the latter the reaction after exposure often begins either immediately or within a short time, whereas in the patient with atopic dermatitis, the reaction may not begin until 12 or 24 hours later so that the relationship thus may be missed entirely. This was demonstrated rather conclusively in our reported

experimental studies in which it was shown that induction of dermatitis or its aggravation which followed either the inhalation of the dust particles by the susceptible patient or the injection of the specific autogenous dust extract, did not take place for at least 12 and in some instances 24 or more hours. These observations explain why parents or the attending physician or allergist often find it difficult to explain exacerbations of dermatitis which are part of a delayed reaction resulting from exposure to an inhalant like house dust.

In the absence of an adequate clinical history suggesting that house dust exposure is etiologically responsible, one must rely upon such evidence as the relief afforded either by removal of the patient to another environment or by specific house-dust desensitization coupled with measures designed to lessen dust exposure. Both these methods have been employed successfully in children with atopic dermatitis to emphasize the etiologic importance of house dust, as illustrated in the following case report.

CASE 1.—A girl, aged 12 years, with flexural atopic dermatitis, recurrent constantly since infancy, and only symptomatically relieved by the usual local dermatologic management. Allergic study showed positive reactions to dust, wool, pollens, and some foods. The patient always improved while at the seashore in the summer. This was attributed to the beneficial effect of the rays of the sun. She was always worse in early fall and winter months. She was asked to go to the seashore in the spring and upon returning to go not to her own home but to the home of a relative in the same neighborhood. The skin condition cleared at the seashore. It did not recur even in a neighboring home of a relative, but became worse within a day or two after returning to her own home. Institution of proper dust precautions and desensitization with an autogenous dust extract in addition to pollen therapy has been followed by marked improvement which has persisted for more than three years. It was subsequently determined by clinical trial that none of the positive-reacting foods, with the possible exception of chocolate, were of etiological significance.

Here then is an example, illustrative of others, of a patient with atopic dermatitis throughout her entire childhood apparently due to sensitivity to her own enviromental dust and improved remarkably by avoidance of contact plus dust desensitization.

The question arises as to whether the house dust excitant can act in these patients not only by inhalation but also by direct contact. Since the lesions often involve the flexures in most patients and they usually are covered, it is unlikely that the dust allergen will have much opportunity to act directly unless large amounts of dust come into direct contact with the skin. This was demonstrated clearly in one of our adult patients with hay fever, asthma, and atopic dermatitis. She observed that when she dusted around the house with a cloth and enough dust came into direct contact with her skin, it caused marked itching and local eruption in the flexural area. But if she inhaled the dust when the flexures were covered, it first would cause her to sneeze and wheeze and then, if the reaction was sufficiently intense, an itching eruption would appear in the affected flexures. Strict avoidance of dust contact together with injections of dust extract has enabled this patient to remain relatively free of dermatitis for more than 10 years, although she has slight asthmatic recurrences at infrequent intervals. It is obvious from this evidence that regardless of the manner of operation, house dust can be and often is an important excitant in atopic dermatitis not only in adults but also in children and that in the latter it probably produces its effects through inhalation.

PLANT POLLENS

As previously mentioned, the importance of plant pollens in the causation of atopic dermatitis had been suggested in earlier clinical reports, notably those of Cazort,[7] Feinberg,[12] and Rowe,[8] even though scant attention was paid to them by other allergists. In my first report, in 1949, emphasizing the importance of inhalant allergens in atopic dermatitis, an unusually high incidence of positive skin-test reactions to pollens, especially ragweed, was noted. This was confirmed in a subsequent study [12] concerning the role of seasonal inhalants like ragweed.

Of the total of 136 patients (68 being less than 12 years old) comprising the material for this study, 88.9% showed positive reactions to ragweed, 58% in moderate to marked degree. In explanation of the positive ragweed reaction, we demonstrated that the ragweed sensitivity in many patients was responsible for seasonal outbreaks of dermatitis, occurring either alone or with concomitant seasonal hay fever. We also proved this clinical relationship experimentally by the induction of dermatitis both following the inhalation of ragweed pollen and after the injection of ragweed pollen extract, either intentionally or accidentally. While most of these observations concerned ragweed pollen, it was found true of other pollens, notably the spring grasses and English plantain, both of which are clinically less important in our region not only in atopic dermatitis but also in hay fever.

As might be expected, similar findings were obtained when the group of 76 children included in the present study were analyzed with relation to pollen sensitivity, especially ragweed. Thus 63, or 82.9%, of the total showed positive reactions to ragweed, 48.7% in moderate to marked degree. As will be noted in Table 2, the incidence of positive reactions to timothy grass and English plantain pollens was much lower than to ragweed, which is similar to that observed in hay fever patients.

As in the previous study, an attempt also was made to determine the basis for the positive skin-test reaction to ragweed in the 63 children in this series; that is, whether the ragweed sensitivity was responsible alone for the dermatitis or whether it was associated with a seasonal hay fever and/or asthma. In the latter instance it could be responsible for both the respiratory and the skin symptoms or solely for the respiratory symptoms, the dermatitis being provoked by other allergens. The results of this analysis are shown in Table 3.

As can be seen from inspection of Table 3, seventeen of the group had perennial atopic dermatitis from various causes (foods and inhalants), with seasonal outbreaks during the ragweed season. Seven of the seventeen had concomitant seasonal hay fever symptoms, usually mild, two had seasonal hay fever and asthma, and four had perennial asthma. The remaining four had seasonal outbreaks without any associated respiratory symptoms.

Of the 46 patients with perennial atopic dermatitis and no seasonal aggravation, 10 had concomitant hay fever and/or asthma to account for the positive ragweed reaction, 22 had perennial asthma, and the other 14 had no associated hay fever or asthma.

It usually is easy to explain a positive skin reaction in a patient who has a seasonal aggravation of a perennial atopic dermatitis with or without concomitant respiratory symptoms. But if there is no seasonal dermatitis or associated hay fever, the positive reaction then must be regarded as a nonclinical positive, that is, one with no proved clinical significance. As previously demonstrated,[12] such a reaction sometimes represents the first evidence of the future development of hay fever in that patient, the skin being the initial tissue to be sensitized. This supposition is strengthened first by the fact that a family history of allergy, especially hay fever, often is obtained in these patients and secondly the fact that as shown by subsequent clinical observation, some patients later develop ragweed hay fever. This is illustrated in these case reports.

TABLE 3.—*Analysis of Sixty-Three Positive Ragweed Reactions*

Nature of Dermatitis	Associated Ragweed Hay Fever and/or Asthma	No Associated Hay Fever
Perennial with seasonal aggravation....	13	4
Perennial with no seasonal aggravation.	32	14
Total.....	45	18

CASE 2.—A girl, aged 5 years, first seen at the age of 2 years, with atopic dermatitis present since infancy. Parents were told by their pediatrician "that child would grow out of it," and only local applications were prescribed. Family history was strongly positive for allergy. Positive skin reactions were obtained to house dust, wool, ragweed,

milk, and a few other foods. The condition was greatly improved by eliminating milk and wool, also by minimizing house-dust contact and by going to the seashore. When first seen, the patient had no hay fever symptoms, nor was there any flare-up during the ragweed season despite a definite positive skin reaction. But for the first time, while at the seashore in August, 1949, she had mild hay fever symptoms which were accompanied by a mild outbreak of atopic dermatitis.

CASE 3.—A 3-year-old girl was first seen in April, 1947, with flexural atopic dermatitis involving the antecubitals, wrists, popliteals and present constantly since the age of 18 months, with no apparent seasonal aggravation. Intracutaneous skin tests were positive to such inhalants as house dust, feathers, orris root, and wool, to several foods, and in slight degree to ragweed pollen, despite the absence of clinical hay fever. After the elimination of the test-positive foods and avoidance of the offending inhalants (notably wool) the eruption disappeared so that specific desensitization was considered unnecessary. In September, 1951, the patient developed typical symptoms of ragweed hay fever associated with mild wheezing which responded to routine symptomatic treatment.

In both of these patients the positive reaction to ragweed pollen antedated the onset of clinical hay fever symptoms; in the first case by about three years and in the second by four years. If such patients are seen at the time they have the dermatitis and no clinical hay fever, the positive pollen reaction may represent either a future or potential pollen reactor which as in the second case had no etiologic relationship to the dermatitis or as in the first case was related to both the dermatitis and the hay fever.

We obviously could not determine how many of the patients with unexplained positive ragweed reactions were of the future clinical positive type. But since 40 of the 63 children came of families in which there was atopic dermatitis, 15 of which had histories of hay fever, this does not seem an unlikely possibility.

From the evidence thus far presented, it seems clear, therefore, that a positive skin-test reaction to ragweed pollen obtained in children with atopic dermatitis sometimes is unrelated etiologically to the dermatitis, but may be due to an associated hay fever, either present at the time the patient is seen or appearing some time in the future. The dermatitis in such patients is due to other nonpollen factors. But in other patients, the pollen sensitivity is definitely related etiologically to the dermatitis. This was true in the 17 children with seasonal outbreaks of atopic dermatitis, 13 of whom had associated hay fever. The remaining four patients had perennial dermatitis from various nonpollen causes, but developed seasonal aggravation of the dermatitis because of an additional allergy to ragweed pollen.

Further evidence of the etiologic importance of ragweed pollen was furnished in our previously reported study [12] by the induction of the dermatitis both by inhalation of dry ragweed pollen and by injection of ragweed pollen extract into susceptible subjects. The latter was done deliberately in two volunteer patients but it also was accidentally induced in others as part of a constitutional reaction following the injection of pollen extract in these patients. This is illustrated in the following case report.

CASE 4.—A girl, aged 6 years, first seen late September, 1948, because of seasonal hay fever and perennial allergic rhinitis of three years' duration. She had "eczema" during infancy, but this disappeared during her second year of life. Pollen therapy was begun on April 26, 1949. On June 6, 1949, the patient on two occasions developed an itching papular eruption in the antecubital, thigh, and chest regions after the injection of ragweed pollen extract in small dosage (0.0006 N), necessitating reduction in dosage. The eruption finally disappeared but recurred in mid-September in the antecubital, thigh, and popliteal areas and persisted for about two months. At that time, the mother recalled that at about the same time during the previous hay fever season (1948), before the child had received treatment, a similar eruption attributed to "prickly heat" had occurred but was milder and of shorter duration. There was no further recurrence of the eruption either during 1950, 1951, 1952, or 1953, while the child was given pollen therapy, and only mild hay fever symptoms were experienced.

This case report illustrates the induction of dermatitis after ragweed injections; also seasonal outbreaks of atopic dermatitis in patients with seasonal hay fever which may be missed unless one is on the alert for it.

Appreciation of the possible role of pollen sensitivity in atopic dermatitis therefore is essential to the proper management of these patients. If a causal relationship can be established by history or by skin-test findings or both, pollen desensitization is definitely beneficial. In the absence of a definite history of seasonal aggravation but with positive skin-test reactions to pollen, it is difficult to decide whether pollen therapy is advisable. If the child has a positive family history of hay fever or mild nasal symptoms, pollen therapy may be helpful prophylactically even if the pollen sensitivity has no bearing on the skin condition, and from long personal experience with its use I am sure that it has been beneficial to many children.

ATMOSPHERIC MOLDS

As already indicated, atmospheric molds also may be important inhalant excitants of atopic dermatitis. This is especially true in those regions in which these inhalants are prevalent, as, for example, the Midwestern, or grain, areas of the United States. In our particular locality, the incidence of mold allergy in hay fever or asthma patients is rather low (only about 5%), and, by inference, this probably also is true of atopic dermatitis. Thus, of the 63 children tested with Alternaria, only 17 had positive reactions, 9 being in moderate to marked degree. While some of these positive reactions undoubtedly were clinically important, it was much harder to establish an etiologic relationship in these patients than in those positive to pollens. However, in our experimental studies, we were able to induce outbreaks of atopic dermatitis in one patient after the inhalation of powdered Alternaria [10] and also by injection of its extract, proving a causal relationship. On the basis of these findings, atmospheric molds must be considered possible excitants of atopic dermatitis, particularly in areas in which they prevail, and should be included in the management of these patients, especially when employing desensitization procedures as with plant pollens.

ANIMAL DANDERS

Animal danders also may be important causes in atopic dermatitis, but, as in asthma, the exact incidence is difficult to estimate. Thus many children had slight or moderately positive skin-test reactions to feather extracts. But it was not easy in those instances to decide whether such reactions were clinically significant, chiefly because feather extracts often give nonclinical positive reactions and also because a clinical relationship cannot be easily proved. These patients probably do not inhale enough feather allergen to produce atopic skin manifestations; nevertheless, feather allergens may be additional excitants. Other danders, including horse, rabbit, cat, and dog, are not prominent causes of atopic dermatitis probably because of lessened opportunity for contact. From 10 to 15% of the patients studied gave positive skin reactions to extracts of these danders; however, in two children definite itching of the affected skin areas or new outbreaks followed contact with a horse; in one, contact with a dog, and in another, being near a cat. In these patients improvement in the skin condition was noted after avoidance of contact with the animals. As in asthma, positive skin tests with extracts of cat, dog, horse, or rabbit epithelium are quite specific. If obtained in a patient with atopic dermatitis, one should search diligently for possible sources of contact.

The importance of wool as an etiologic factor in atopic dermatitis is unquestioned. But whether wool acts as an inhalant or as a contactant allergen or whether it causes aggravation by nonspecific irritation is not always easy to determine. Thus 26 of the 76 children studied stated definitely that they could not tolerate wool contact, that itching of the skin or actual eruption followed when wool was brought into contact with their skin lesions or even with the unaffected skin. Undoubtedly, in some of these patients a direct contactant and perhaps irritant effect is responsible, and perhaps the eruption in these instances is not due to specific sensitization. Nevertheless, many patients showed definite improvement when the woolen arti-

cles of clothing or bedding or woolen rugs were removed completely. Since these are not always in direct contact with the patient's lesions, one may assume that some of the wool allergen entered the circulation after being inhaled. As with feathers, the incidence of positive skin tests with wool extract usually is high (63.2% of the 76 children) but is not always indicative of specific sensitization. However, regardless of the mechanism, wool is an important allergenic factor, so that it is essential for all patients with atopic dermatitis to eliminate wool contacts.

A similar situation exists in relation to silk. Patients with atopic dermatitis may show positive skin reactions to this allergen. About one-fourth of the children tested showed positive skin reactions, four in moderate degree. But none were aware of any evidence of clinical sensitivity, which is not easy to detect. As previously mentioned, evidence that silk can be responsible for aggravation of symptoms in patients with atopic dermatitis already has been furnished by others.† As with wool, although it generally is believed that the allergic reaction is provoked by direct contact of the silk with the patient's skin, the experiments of Sulzberger and Vaughan [6] conclusively demonstrate that silk protein when inhaled is absorbed into the circulation and thus can aggravate or induce the lesions of atopic dermatitis. It is not easy to determine in a silk-sensitive patient which route is operative. Patch tests usually are negative, but this does not exclude a possible contactant action. Regardless of the mode of action, it is advisable to remove all possible sources of silk contact in children with positive skin-test reactions to silk.

Other inhalant allergens, like orris root, tobacco, insecticides, goat hair, and cereal flours, are possible but infrequent causes of atopic dermatitis, especially in children. Thus, for example, occasional instances have been reported of atopic dermatitis in adults secondary to inhalation of cereal flours, especially in bakers, but this obviously would not apply in children. Even the inhalation of the odors of cooking,[14] especially of fish, or of perfume or highly scented cosmetics may cause aggravation in some patients. Interest again has been revived in the possibility that sensitivity to human dander may be a causative factor in atopic dermatitis, especially in infancy. Allergy to human dander first was described in 1925, by Van Leeweun, in Holland, who considered it important in bronchial asthma. But this was never clearly proved, and the subject was dropped. Recently, Simon [15] showed that infants with atopic dermatitis gave positive skin reactions and passive transfer tests to human dander. He believes that in such instances the human dander present in the scalp of the mother or father may aggravate the lesion, especially in infants, either from direct contact with the skin or possibly from inhalation. No definite etiologic relationship has been established as yet in these patients. Until it is, one must withhold judgment as to the possibility that human dander is a specific causative inhalant factor in atopic dermatitis, although it does no harm to take precautionary steps with the parents of the affected children.

CLINICAL MANAGEMENT

Knowledge of the implication of inhalant allergens as causative agents in atopic dermatitis affecting children is essential to the clinical management of these patients. This is particularly applicable to those patients, especially older children, who fail to improve after the elimination of test-positive food reactors, a procedure which in infants or young children sometimes is followed by remarkable improvement in the dermatitis or its complete disappearance. When this does not happen or the improvement is slight or temporary, an inhalant etiology should be sought. Indication of the possible etiologic significance of inhalant allergens in these cases may be furnished if specific positive skin-test reactions are obtained. However, corroboration by clinical evidence is even more important. A striking example is the improvement in the dermatitis which follows change of residence or hospitalization in dust-

† References 5 and 6.

sensitive patients or that which sometimes follows desensitization with extracts of offending inhalants, like pollens, molds, or house dust. More definite proof of the causal relationship could be furnished by induction of the dermatitis following inhalation of the suspected inhalant, but this is not often possible or practical, especially in patients with concomitant respiratory allergies.

Actually, treatment of children with atopic dermatitis would be greatly simplified if it were approached as though the patient has asthma instead of dermatitis. Thus we routinely skin test these patients, even infants, not only with extracts of foods but also with important inhalant allergens like house dust, molds, wool, animal danders, and common pollens. If positive reactions are obtained, efforts are made whenever possible to establish their specificity or clinical importance. In either case, elimination of the offending inhalant allergens is carried out. This is just as important for patients with atopic dermatitis as it is in asthmatics. This may be easy with allergens like feathers or animal danders or difficult with others, such as house dust or pollens. If wool is a factor, substitutes should be provided (e. g., a cotton quilt for a woolen blanket or cotton or rayon sweaters instead of wool) or the wool should be covered in such a manner as to prevent its coming into direct contact with the skin or from being inhaled (as by lining woolen snowsuits for children with cotton sheeting). When inhalant contact cannot be completely avoided, specific desensitization may be necessary. This is true especially with regard to house dust, pollens, and molds. Desensitization with extracts of animal danders or wool is not too effective but seldom is necessary. Treatment with allergenic extracts of these inhalants is given in the same way (and for the same length of time) as in asthmatics, except that smaller and at times minute doses must be given in order to avoid the induction of constitutional reactions. The latter appear much more slowly in dermatitis patients than in patients with asthma or hay fever and are indicated usually by aggravation of an already existing dermatitis rather than by an acute flare-up. For example, in several children who were being given injections of an autogenous house-dust extract, when the point of maximum tolerance was reached, further injections were followed in a day or two by new outbreaks of dermatitis. The injections were discontinued, and the reaction subsided. Later the injections were started again in lower dosage and were better tolerated.

It is extremely important for the attending physician to recognize the delayed nature of reactions to these injections which might be responsible not only for aggravation of the dermatitis but also for its persistence. Reactions can be avoided by reduction of the dosage to a point—often rather minute—at which they no longer are induced. We also recently have minimized this tendency to reaction by giving the injections intracutaneously, using amounts not over 0.1 or 0.15 cc. and varying the concentrations of the extract.

CONCLUSIONS

Inhalant allergens, especially house dust, plant pollens, atmospheric molds, and wool, can be just as important excitants of atopic dermatitis in children as of asthma. Failure to appreciate this has been responsible for the seeming intractability of some of these patients, whereas their detection and correction often will be followed by noticeable and lasting improvement. All children, no matter how young, who have atopic dermatitis therefore should be investigated routinely not only for possible food allergy but also for inhalant allergies and treated accordingly. Consideration of the importance of inhalant allergy and its inclusion in the clinical management of these patients will be rewarded by much more success in treatment than has been previously obtained.

REFERENCES

1. Sulzberger, M. B., and Coca, A. F., in Sulzberger, M. B.: Dermatologic Allergy: An Introduction in the Form of a Series of Lectures, Springfield, Ill., Charles C Thomas, Publisher, 1940.

2. Hill, L. W.: Chronic Atopic Eczema (Neurodermatitis) in Childhood, J. A. M. A. **103**:1430, 1934.

3. Cooke, R. A.: Allergy in Theory and Practice, Philadelphia, W. B. Saunders Company, 1947.

4. Walker, I. C.: Causation of Eczema, Urticaria and Angioneurotic Edema by Proteins other than Those Derived from Food: Study XVIII, J. A. M. A. **70**:897, 1918.

5. Figley, K. D., and Parkhurst, H. J.: Silk Sensitivity, with Especial Reference to Its Rôle in Atopic Eczema, J. Allergy **5**:60, 1933.

6. Sulzberger, M. B., and Vaughan, W. T.: Experiments in Silk Hypersensitivity and the Inhalation of Allergen in Atopic Dermatitis (Neurodermatitis Disseminatus), J. Allergy, **5**:554, 1934.

7. Cazort, A. G.: The House Dust Antigen in Allergy, South. M. J. **29**:1022, 1936.

8. Rowe, A. H.: Dermatitis of the Hands Due to Atopic Allergy to Pollen, Arch. Dermat. & Syph. **53**:437, 1946.

9. Tuft, Louis: Importance of Inhalant Allergens in Atopic Dermatitis, J. Invest. Dermat. **12**: 211, 1949.

10. Tuft, L.; Tuft, H. S., and Heck, V. M.: Atopic Dermatitis: I. An Experimental Clinical Study of the Role of Inhalant Allergens, J. Allergy **21**:181, 1950.

11. Tuft, L.; Tuft, H. S., and Heck, V. M.: Atopic Dermatitis: II. Role of the Sweating Mechanism, J. Invest. Dermat. **15**:333, 1950.

12. Tuft, L., and Heck, V. M.: Studies in Atopic Dermatitis: IV. Importance of Seasonal Inhalant Allergens, Especially Ragweed, J. Allergy **23**:528, 1952.

13. Feinberg, S. M.: Seasonal Atopic Dermatitis: The Rôle of Inhalant Atopens, Arch. Dermat. & Syph. **40**:200, 1939.

14. Horesh, A. J.: Allergy to Food Odors: Its Relation to the Management of Infantile Eczema, J. Allergy **14**:335, 1943.

15. Simon, Frank A.: The Allergen of Human Dander: Its Relative Concentration in Several Skin Areas and in Appendages, Products and Derivatives of Epidermis, J. Invest. Dermat. **11**:203, 1948.

HEMATURIA AS MANIFESTATION OF SICKLE-CELL ANEMIA IN CHILDREN

ROBERT L. VERNIER, M.D., Little Rock, Ark.

SICKLE-CELL anemia is a congenital and hereditary disease occurring almost exclusively in Negroes. In the United States it has been estimated that between 30,000 and 100,000 persons have the disease.[1] Since the average age of onset of symptoms is 3 to 5 years,[2] the disease presents a problem in pediatric practice.

The symptomatology and pathology of sickle-cell anemia are extremely diverse. Although much has been written regarding its manifestations in the cardiovascular system, the integument, the central nervous system, and the skeletal system, there have been very few reports of its renal manifestations. The current textbooks of hematology and urology fail to mention sickle-cell anemia as an etiologic factor in renal pathology. Recently several articles dealing with hematuria as a manifestation of sickle-cell anemia have appeared in journals of urology and internal medicine, but no such reports have appeared heretofore in the pediatric literature. It was felt that the following case report was therefore justified.

REPORT OF A CASE

M. W., a 5-year-old Negro girl, was born of a normal pregnancy and delivered by Caesarean section without complications. Her development was entirely normal. The only illnesses of her early childhood were whooping cough at 3 years of age and occasional bouts of tonsillitis. The mother had been told by a physician that the child had a "leaking heart." The father died at the age of 35 years of "high blood pressure." The mother is well. There is no family history of bleeding tendencies, anemia, heart disease, or renal disease. There are no other children in the family.

Department of Pediatrics, University of Arkansas School of Medicine.

On Aug. 1, 1952, approximately three weeks prior to her admission to the University Hospital, the child had what her mother called "an upset stomach," characterized by fever, intermittent right-sided abdominal pain, and vomiting. A physician was consulted who treated her with "shots" daily for five days with prompt relief of all symptoms. She remained well until Aug. 12, 1952, ten days prior to admission, when while playing she fell, striking her right side against a bench. After this trauma she cried for a short time with pain in her side. The mother took little note of the incident and was able to recall the injury only after prolonged questioning.

Four days after the injury, or six days prior to admission, the child called her mother's attention to the fact that her urine was bloody. There was no dysuria, frequency, or other urinary tract symptoms at that time. Her urine was grossly bloody and contained clots each time she voided thereafter. A local physician was consulted. He reported that the physical examination at that time revealed only slight tenderness to deep palpation in the right upper quadrant. The child's urine was cloudy red in appearance, alkaline in reaction, with a specific gravity of 1.022; the albumin was 1+, and the test for glucose was negative. Red blood cells were too numerous to count, and white blood cells were occasionally seen on microscopic examination. The physician told the mother that the child had a "kidney and bladder infection." Penicillin injections and an alkalinizing solution were prescribed. The physician saw the patient daily thereafter for six days. On Aug. 18, 1952, the patient complained of pain in her right side and lower abdomen. She had a slight fever at the time and was again tender to palpation in the right flank. The fever lasted only 24 hours. Hematuria, with the passage of clots of blood, continued daily for the next five days. Intermittent right-sided pain of varying intensity occurred daily. Examination of urine specimens revealed a somewhat variable red coloring, but red blood cells were consistently too numerous to count on microscopic examination. The patient vomited on one occasion, the day of admission.

On admission to the University Hospital physical examination revealed a well-developed well-nourished girl in no acute distress. She was alert and cooperative. Her temperature was normal. There was no icterus of the sclerae. There were numerous dental cavities. The heart seemed enlarged slightly

to the left of the midclavicular line. There was a loud high-pitched systolic murmur, heard best in the third left interspace, at the left sternal border. The blood pressure was 110/70 mm. Hg. The femoral vessels were palpable. The liver was palpable at the right costal margin. Slight tenderness and voluntary guarding to deep palpation in the right upper quadrant of the abdomen were found. The external genitalia were normal without evidence of fissure, ulceration, or erythema of the urinary meatus. The hemoglobin on admission was 6.5 gm. per 100 cc. of blood. The red blood cell count was 1,840,000, and the cells were hypochromic and showed anisocytosis and poikilocytosis. The white blood cell count was 14,400, with a normal differential count. There were 4 nucleated red blood cells per 100 white blood cells. A sickle-cell preparation showed 10% sickling in 30 minutes (wet mount preparation with 2% sodium bisulfite added). The bleeding time was 2 minutes 45 seconds. The clotting time was three minutes (Lee-White method). The prothrombin time was 18.2 seconds (52% of normal prothrombin activity.) The alkali-resistant hemoglobin fraction was 8.34%. The admission urine specimen was grossly bloody. The specific gravity was 1.008, albumin 3+, and sugar negative. Microscopic examination revealed too many red blood cells to count and occasional white blood cells, crystals, and epithelial cells. A hemoglobin test on the urine specimen (standard photoelectric hemoglobin technique) showed 0.9 gm. per 100 cc. The serum nonprotein nitrogen was 27.5 mg. per 100 cc. A plain x-ray film of the abdomen revealed coarsening of the trabecular pattern of both iliac bones and a slight sclerosis of the bones of the ribs. These findings were thought to be suggestive of a blood dyscrasia. X-ray studies of the chest and heart revealed slight generalized cardiac enlargement. Routine x-ray studies of the bones of the skull and extremities were considered normal. Intravenous pyelograms demonstrated slight dilatation of the right kidney calyces and pelvis. The outlines were not clearly seen, and the area appeared to be occupied by a negative type cast interpreted as clot formation. The left urinary tract was thought to be normal.

The patient was given a blood transfusion of 500 cc. of whole blood shortly after admission. Urine specimens were grossly bloody for the first 36 hospital hours, or until Aug. 25, 1952, when clear yellow urine with no abnormalities was obtained. The child's hemoglobin had risen to 10.3 gm. per 100 cc. at this time.

Cystoscopy and retrograde pyelography were done by the urologist, Dr. James Headstream, on Aug. 27, 1952. The bladder was normal, and clear urine was seen coming from both ureteral openings. A retrograde pyelogram was normal; the previously described filling defects in the right renal pelvis had disappeared. The patient was discharged on Aug. 29, 1952.

The child was again seen on Oct. 8, 1952, one month after discharge. There had been no recurrence of symptoms and no illness of any kind. Physical examination at that time contributed no new information. A urinalysis was entirely normal. Her hemoglobin was 8.7 gm. per 100 cc.

She was again seen on March 5, 1954, at which time no history of recurrence of the previous symptoms was obtained. She had had two bouts of mild abdominal pain during the summer of 1953, and epistaxis had occurred on two occasions in the interval since discharge. She had grown well and presented essentially the same physical findings as upon discharge. Laboratory studies at this time revealed a normal urine, a hemoglobin of 7.8 gm. per 100 cc., red blood cell count of 2,530,000, white blood cell count of 20,700, and a normal differential count except for the presence of 6 nucleated red blood cells per 100 white blood cells. A sickle-cell preparation showed 50% sickling of the red blood cells in 30 minutes (wet mount, sodium bisulfite method). The alkali-resistant hemoglobin fraction was 5.4%. The direct serum bilirubin was 0.26 mg. per 100 cc., and the indirect serum bilirubin (30 minutes) 2.74 mg. The total serum bilirubin was 3.0 mg. per 100 cc.

Studies of the patient's mother for evidence of sickle-cell anemia or the sickling trait were undertaken. The mother's hemoglobin was 13.0 gm. per 100 cc. A sickle-cell preparation was negative at 30 minutes. Her alkali-resistant hemoglobin fraction was 2.0%.

COMMENT

Hematuria whenever it occurs in children is a distressing and significant sign of pathology. Campbell, in his textbook of pediatric urology,[3] cites over 50 causes of hematuria in childhood, many of which, however, result only in microscopic hematuria. Profuse gross hematuria is said to be rare except in association with renal injury. In discussing the etiology of hematuria, most textbooks of urology include as a large category "essential hematuria." In recent years several articles have been published which suggest that in some cases of "essential hematuria" the hematuria is a manifestation of sickle-cell disease.* The Table, a review of the literature, reveals a total of 29 reported cases of hematuria occurring in patients with the

* References 4-10.

Cases of Hematuria and Sickled Red Cells Compiled from the Literature

Author	Age, Yr.	Sex	Duration	Hematologic Data	
Abel [4]	23	M	5 mo.	S. test * neg. % HGB. 81%	I. V. P. revealed filling defect in left renal pelvis; nephrectomy; no tumor found; renal vessels filled with sickled cells, some vessels partially necrotic
Goodwin [8]	19	M	3 mo.	S. test + RBC 2,000,000	I. V. P. revealed filling defects in left renal pelvis; nephrectomy; renal vessels filled with sickled RBC; clinical findings compatible with sickle-cell disease
	34	M	3 mo.	No S. test HGB. 12 gm.	Explored for tumor; patient died; autopsy revealed submucosal hemorrhages in right renal pelvis; numerous sickle cells in renal vessels; sickle-cell trait
	11	M	2 wk.	S. test 100% HGB. 5.7-10 gm.	Normal I. V. P.; treated conservatively, hematuria recurred in 7 mo.; site, left kidney; trait only (?)
	23	F	3 days	S. test + HGB. 8.4 gm.	Six previous bouts of hematuria; clinical findings of sickle-cell anemia; conservative therapy
	44	F	.....	"Not anemic" S. test 35%	Three bouts of hematuria and renal colic; conservative therapy; trait only (?)
	34	M	6 wk.	S. test 100% HGB. 11 gm.	Hematuria from left ureteral orifice; conservative therapy; sickle-cell trait (?)
	41	F	4 days	No S. test HGB. 40%	Hysterectomy; sickle cells noted in uterine vessels; probable sickle-cell trait only
Creecy [5]	22	M	4 wk.	S. test + HGB. 75%	I. V. and retrograde pyelograms normal; left nephrectomy; renal vessels congested with sickle cells; trait only
	54	M	3 mo.	S. test + HGB. 80%	I. V. P. revealed calculus in right renal pelvis; hematuria ceased in 2 wk. with conservative therapy; clinical diagnosis of sickle-cell anemia
Fetter [6]	62	M	1 wk.	S. test 90% HGB. 10 gm.	Unexplained hematuria at age 49; I. V. P. revealed filling defect on the left, conservative therapy; trait only
Harrison † [7]	42	M	23 days	S. test + HGB. 9-12 gm.	Left ureteral bleeding on cystoscopic examination; left nephrectomy; submucosal hemorrhages of papillae; dilated vessels filled with sickle cells; trait only
	33	M	4 mo.	S. test + HGB. 12 gm.	Left ureteral bleeding on cystoscopic examination; left nephrectomy; congestion of vessels with sickle cells; trait only
	28	F	5 days	S. test 30% HGB. 12 gm.	Unexplained hematuria 7 yr. earlier; left ureteral bleeding; left nephrectomy; trait only (?)
	31	F	5 days	S. test + HGB. 10 gm.	Bleeding noted from right ureteral orifice; right nephrectomy; clinical diagnosis of sickle-cell anemia
Ryan [9]	21	M	2 mo.	S. test + HGB. 15 gm.	Normal urologic studies except for right ureteral bleeding; nephrectomy; glomeruli and tubules congested with sickle cells
	24	F	1 wk.	S. test + HGB. 13.5 gm.	Site of bleeding not determined; autopsy revealed widespread hemorrhage into internal organs; renal vessels congested with sickle cells; collecting tubules contained heme casts
Lund [10]	43	M	10 days	S. test + HGB. 13 gm. A.R.H. normal ‡	Unexplained hematuria 5 yr. earlier; pyelograms normal; left ureteral bleeding noted; left nephrectomy; congestion of vessels, hemorrhage, and hemosiderosis noted on microscopic examination; hematuria recurred 4 yr. later
	27	F	3 days	S. test + HGB. normal A.R.H. normal	Normal pyelograms; left ureteral bleeding; conservative therapy
	54	M	2 wk.	S. test + HGB. 15 gm. A.R.H. normal	Normal pyelograms; left ureteral bleeding; left nephrectomy; vessels engorged with sickle cells; areas of hemorrhage in the parenchyma and pelvis
	32	M	5 days	S. test + HGB. 11 gm. A.R.H. normal	Normal pyelograms; left ureteral bleeding; conservative therapy
	35	M	3 wk.	S. test + HGB. normal A.R.H. normal	Right-sided ureteral bleeding; ceased abruptly with conservative therapy
	35	M	5 days	S. test + HGB. normal A.R.H. normal	Normal pyelograms; left ureteral bleeding on cystoscopic examination; spontaneous recovery
	31	M	4 days	S. test + HGB. normal A.R.H. normal	Normal pyelograms; left ureteral bleeding on cystoscopic examination; spontaneous recovery

* S test indicates test for sickle cells.

† Five additional patients reported, all of whom had unilateral (4 left-sided) hematuria. All had positive sickle tests. One patient was thought to have sickle-cell anemia. All were treated symptomatically with recovery. Details lacking.

‡ Test for alkali-resistant hemoglobin. Note is made as to the existence of sickle-cell trait or sickle-cell anemia in each patient according to the author's impression.

erythrocyte sickling phenomenon. The patients were studied extensively in an attempt to explain the hematuria by some other mechanism. No other explanation was found even in the eight patients in whom nephrectomy was performed. Twenty-one of the patients were believed to have only the sickling trait without anemia; five had clinical sickle-cell anemia. In three cases the sickling phenomenon was not demonstrated in vivo but was later demonstrated in the organs studied microscopically following operation or autopsy. In eight of the patients nephrectomy was done either because of suspected renal neoplasm or because of persistent hematuria which continued despite conservative therapy. No specific cause for the hematuria could be found in the kidneys studied microscopically after nephrectomy. Characteristically, the microscopic studies revealed congestion of the renal vessels with sickled red blood cells and hemorrhage into the submucosa and mucosa of the renal pelvis. Occasionally the vessels near the mucosal surface were partially necrotic. Thrombosis of the renal vessels was found only rarely. In one of the cases described by Ryan and Fuller,[9] there was congestion of the glomeruli with escape of sickled red blood cells into the periglomerular space and the renal tubules. It was the author's opinion that this capillary defect was the major source of the hematuria. Congestion of blood vessels, hemosiderosis, thrombosis, and ischemic infarction in various organs of the body have been described by Diggs and Ching[11] as characteristic of sickle-cell anemia. Kimmelstiel[12] points out that the tissues at autopsy reveal few thrombi. He suggests that tissue anoxia resulting in capillary stasis and engorgement with eventual ischemic necrosis of the organs involved explains many of the pathologic findings. Most authors agree that sickled red blood cells, which have increased rigidity and bizzare shapes, may logically have difficulty passing through small vessels, interlock and lodge, leading to stasis, congestion, and possibly thrombosis. In such instances the vessel wall might be altered functionally and its permeability increased to such an extent that cellular elements of the blood could pass into the parenchymal tissues and, in the kidney, result in hematuria. Kunz and co-workers[13] have recently reported decreased urinary concentrating ability in a series of children with sickle-cell anemia. They suggest that ischemic changes and thrombosis of vascular elements of the renal parenchyma probably explain the changes in tubular function.

The fact that the renal hemorrhage in the cases of hematuria reported has been unilateral in every instance and restricted to the left kidney in the majority of cases is difficult to explain. It may be that some anatomical or developmental difference predisposes the left kidney to more anoxia than the right and thus the sickling phenomenon and its consequences are increased in severity on that side.

It is interesting that only five of the patients with hematuria and sickled red blood cells have apparently had sickle-cell anemia. However, definitive studies of the nature of the hemoglobin present in the red blood cells of the various patients have not been carried out except in those of Lund. Bauer and Fisher[14] emphasized that the clinical manifestations of sickle-cell disease may be present in the absence of anemia and states that the main threat to life is not the anemia but the capillary stasis occasioned by intravascular sickling. He reported a number of patients in whom death occurred as a result of generalized capillary plugging before anemia was manifest.

SUMMARY

A case of hematuria in a 5-year-old child who was shown to have sickle-cell anemia and in whom no other cause for hematuria could be demonstrated is presented. The literature regarding hematuria as a manifestation of sickle-cell anemia is briefly reviewed. Various theories as to the pathology and etiology of the hematuria and its significance are discussed.

REFERENCES

1. Mercer, R. D.: Recent Developments in Sickle Cell Anemia, Postgrad. Med. **13**:224-227 (March) 1953.

2. Scott, R. B.; Banks, L. O.; Jenkins, M. E., and Crawford, R. P.: Studies in Sickle-Cell Anemia: Clinical Manifestations of Sickle-Cell Anemia in Children (Analysis of 37 cases with Observations on Use of ACTH and Cortisone in 2 Additional Cases), J. Pediat. **39**:460-471 (Oct.) 1951.

3. Campbell, M.: Clinical Pediatric Urology, Philadelphia, W. B. Saunders Company, 1951, p. 5.

4. Abel, M. S., and Brown, C. R.: Sickle Cell Disease with Severe Hematuria Simulating Renal Neoplasm, J. A. M. A. **136**:624-625 (Feb. 28) 1948.

5. Creecy, A. A.; Varano, N. R., and Hurdle, T. G.: Hematuria as a Manifestation of Sickle Cell Disease, Virginia M. Month. **78**:642-645 (Dec.) 1951.

6. Fetter, F., and Schnabel, T. G.: Sickle-Cell Anemia in Patients over 45: Report of 2 Cases, Geriatrics **4**:309-314 (Sept.-Oct.) 1949.

7. Harrison, F. G., and Harrison, F. G., Jr.: Hematuria with Sickle Cell Disease, J. Urol. **68**:943-949 (Dec.) 1952.

8. Goodwin, W. E.; Alston, E. F., and Semans, J. H.: Hematuria and Sickle Cell Disease: Unexplained, Gross Unilateral, Renal Hematuria in Negroes, Coincident with the Blood Sickling Trait, J. Urol. **63**:79-96 (Jan.) 1950.

9. Ryan, J. E. and Fuller, R. H..: Hemorrhagic Manifestations of Sickle Cell Disease, U. S. Armed Forces M. J. **2**:623-633 (April) 1951.

10. Lund, H. G.; Cordonnier, J. J., and Forbes, K. A.: Gross Hematuria in Sickle Cell Disease, J. Urol. **71**:151-158 (Feb.) 1954.

11. Diggs, L. W., and Ching, R. E.; Pathology of Sickle Cell Anemia, South. M. J. **27**:839-845 (Oct.) 1934.

12. Kimmelstiel, P.: Vascular Occlussion and Ischemic Infarction in Sickle Cell Disease, Am. J. M. Sc. **216**:11-19 (July) 1948.

13. Kunz, H. W.; Pratt, E. L.; Mellin, G. W., and Cheung, M. W.: Impairment of Urinary Concentration in Sickle-Cell Anemia, Pediatrics **13**:352-356 (April) 1954.

14. Bauer, J., and Fisher, L. J.: Sickle Cell Disease, with Special Regard to Its Nonanemic Variety, Arch. Surg. **47**:553-563 (Dec.) 1943.

Case Reports

ACQUIRED HEMOLYTIC ANEMIA

Use of Replacement Transfusion in a Crisis

J. M. BOWMAN, M.D., New York

THE PRESENT-DAY treatment of idiopathic acquired hemolytic anemia centers around the use of corticotropin (ACTH) or cortisone with or without splenectomy. Transfusions are often given, but the results frequently are not such as one hopes for, the transfused cells being rapidly hemolyzed and the patient not improved.

Recently we have had under observation a small child with acquired hemolytic anemia who seemed to be made worse by transfusions, corticotropin, and cortisone. Replacement transfusion produced a dramatic, although temporary, remission, while cortisone alone at a later date brought about a symptomatic cure.

REPORT OF CASE

E. H., a 22-month-old girl, was admitted to the Winnipeg Children's Hospital, July 8, 1953, with a history of recurrent purulent otitis media for 19 months; pallor for 12 months, unresponsiveness to iron; intermittent jaundice for 8 months, deepening with upper respiratory infections; no family history of jaundice or anemia.

On admission the child was pale with an underlying icteric tint. The liver and spleen were enlarged, and there was a profuse purulent discharge from the left ear. Blood studies revealed RBC 1,200,000; Hgb. 4.8 gm. per 100 cc.; hematocrit reading 16.5%; reticulocytes 38%; normoblasts 5%; erythrocyte fragility 73% in 0.52% NaCl; bone marrow, marked erythrogenic hyperplasia; direct Coombs test positive in less than one minute*; bilirubin 4.9 mg. per 100 cc. Urine was negative for hemoglobin. Pneumococci and Hemophilus influenzae were present in the ear discharge. The diagnoses were acquired hemolytic anemia and chronic otitis media. It was thought possible that the infection might bear a causal relationship to the hemolytic anemia.

The child was given penicillin, streptomycin, oxytetracycline (Terramycin) and two transfusions of 250 cc. each of "matched" blood. Corticotropin and then cortisone were started. Her course is set out in detail in Table 1. She became worse. With antibiotics, transfusions, and corticotropin and cortisone being given in the same period, it is impossible to say what was the effect of each, but the combination appeared not to ameliorate but rather to accelerate the course of her disease.

By July 16 (ninth hospital day), she was in desperate straits. Rapid hemolysis was continuing, and her bone marrow was now inactive. Her hemoglobin was 3.4 gm. per 100 cc. In the hope of stopping the hemolysis, it was decided to remove her spleen after one more large transfusion. Because of the rapid destruction of supposedly compatible blood on two previous occasions, the Blood Group Research Laboratory was asked to select the donor bloods for the preoperative transfusion. One hundred twenty bloods, including samples from the two "compatible" donors already used, were tested; her serum agglutinated them all by both the albumin and indirect Coombs techniques. Her own blood group was A, MNs, CDe.cde, kk.

The problem was what to do. Would further transfusion serve to depress the marrow still more, at the same time speeding up the hemolytic process, or would it buoy the patient up enough to allow splenectomy? Replacement transfusion was proposed as an alternative procedure. It was hoped that the replacement, by removing sensitized cells and antibody and supplying a large volume of unsensitized cells, would temporarily slow the hemolytic process and make splenectomy less hazardous. Early on the morning of July 17, over a four-hour period, replacement transfusion was carried out via the long saphenous vein at the fossa ovalis. Two liters of donor blood as closely compatible as possible was used, 20 cc. lots being withdrawn and transfused. At the beginning of the transfusion the patient was white, dyspneic, and restless; at the end she was pink, peaceful, and asleep. Her hemoglobin value had been raised from 2.1 to 10.6 gm; her pulse rate had dropped from 132 to 100; her respirations from 40 to 20.

From the Children's Hospital, Winnipeg, Man., Canada.

Present address: Babies Hospital, Columbia Presbyterian Medical Center.

* The Coombs tests were done by the capillary method of Chown, where the time in which agglutination occurs is roughly inversely proportional to the strength of the reaction, failure to agglutinate within ten minutes denoting a negative test.

TABLE 1.—*Course of Disease to Time of Replacement Transfusion*

Date	HGB., Gm./ 100 Cc.	Reticulocytes	Direct Coombs Test	Bone Marrow	Transfusions Blood	Serum Bilirubin	Urine	Clinical Condition	Antibiotics*	Cortisone and Corticotropin†
7/ 8/53	4.8	38.0	+ Immediate	.....	.....	2.9 direct 4.9 total	Bile + ve HGB. —	Pale, ear discharging; spleen and liver large	D, 1 cc.	.....
7/ 9/53	...	....	.....	Erythroid hyperplasia	250 cc.	.....	.....	.....	D, 1 cc.	.....
7/10/53	8.1	....	.....	.....	.....	.....	Bile + Porphyrins increased	Temp. 104 F.; pallor marked	D, 1 cc. O, 250 mg. I.V.	.....
7/11/53	6.1	....	.....	.....	250 cc.	.....	.....	.....	O, 250 mg. I.V. O, 125 mg. q. 6 h.	.....
7/12/53	...	....	.....	.....	.....	.....	.....	Temp. 104 F.	O, 125 mg. q. 6 h.	A, 10 mg. I.M.
7/13/53	6.7	1.3	.....	.....	.....	.....	HGB. —	Pallor and listlessness increasing	O, 125 mg. q. 6 h.	A, 10 mg. C, 50 mg. × 4 daily
7/14/53	4.3	....	.....	.....	.....	.....	HGB. — Bile +	.....	O, 125 mg. q. 6 h.	C, 50 mg.
7/15/53	3.4	....	.....	.....	.....	0.9 direct 2.75 total	HGB. — Bile +	Refusing food and fluids; ear no longer discharging	O, 125 mg. q. 6 h.	C, 50 mg.
7/16/53	3.4	0.1	+ Immediate	Marked hypocellularity	.....	.....	HGB. —	Refusing food and fluids; ear no longer discharging	O, 125 mg. q. 6 h.	C, 50 mg.
7/17/53 (Pre-exchange)	2.1	6	+ Immediate	.....	2,000 cc.	.....	.....	White, dyspneic restless	O, 125 mg. q. 6 h.	C, 50 mg.
7/17/53 (Post-exchange)	10.6	38	Partial at 6 min.	.....	.....	.....	.....	Pink, peaceful, asleep	O, 125 mg. q. 6 h.	C, 50 mg.

* D indicates Dicrysticin (penicillin-streptomycin preparation); O, oxytetracycline.
† A indicates Acthar Gel (corticotropin); C, cortisone.

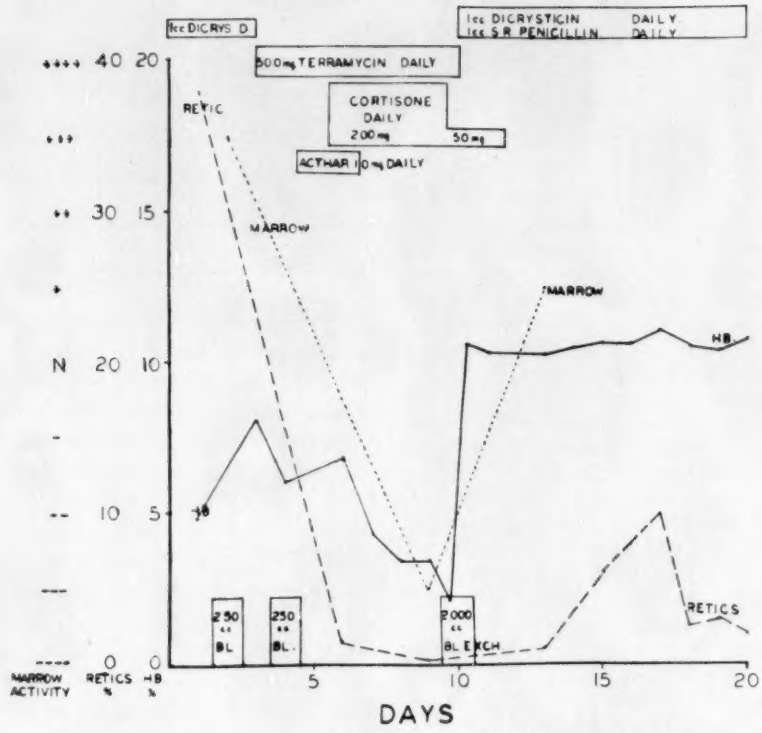


Chart 1.—Course of disease during first hospital admission.

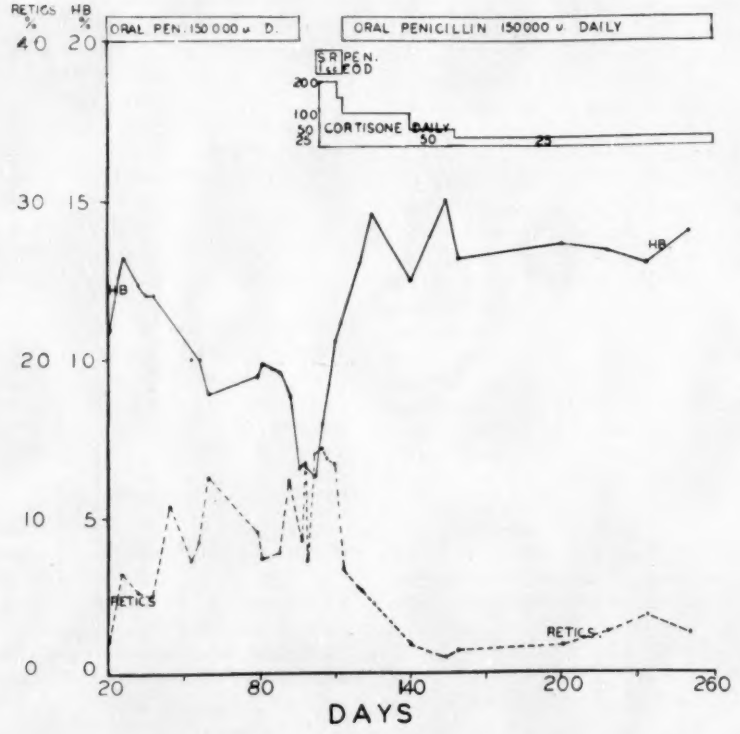


Chart 2.—Course of disease following first admission up to present.

Her pretransfusion Coombs test was instantaneous; her post-transfusion Coombs test was partially positive at six minutes. The cortisone was reduced and then stopped altogether 48 hours after the replacement transfusion, and the child's clinical condition and blood picture watched. Her hemoglobin remained at the post-transfusion level throughout the remainder of July. She was discharged in apparent good health July 30, although her liver and spleen were still palpable and the Coombs test was positive within two minutes.

During August and September her only treatment was oral penicillin, administered to prevent a recurrence of the ear infection. In August her hemoglobin stayed between 12 and 13 gm. per 100 cc. In early September it was 10 gm., dropping to 8.9 gm. Sept. 7 and then stabilizing at about 9.5 gm. until Oct. 9; hemolysis had reappeared but at a slower rate than prior to the replacement transfusion.

On Oct. 5 her family doctor reported that she was mildly jaundiced; there were several cases of infectious hepatitis in the district and one in her own family. She was readmitted to the hospital Oct. 14, moderately jaundiced, pale, and listless, her liver and spleen still enlarged. Her ears appeared normal; Hgb. 6.6 gm. per 100 cc.; reticulocytes 9.1%; serum bilirubin 7.5 mg., mostly direct. There was bilirubinuria. However, normal thymol and cephalin flocculation tests and absence of nausea and vomiting were against the diagnosis of infectious hepatitis or homologous serum jaundice. Oct. 16 her hemoglobin was 6.3 gm. per 100 cc. and her Coombs test was positive within one minute. Oct. 19 her jaundice was deepening and her liver was larger and quite firm.

Before resorting to a second replacement transfusion and then to splenectomy in an effort to curb the hemolysis, further trial with cortisone was decided upon. A response was observed almost at once. In two days her hemoglobin value was 7.9 gm. per 100 cc., and five days later, 10.6 gm. For a day or two her jaundice deepened, then it faded rapidly and was gone within seven days of start-

TABLE 2.—*Course of Disease from Replacement Transfusion to Second Admission*

Date	Hgb., Gm./ 100 Cc.	Reticulocytes	Coombs Test	Bone Marrow	Clinical Condition	Antibiotics	Cortisone
7/17 (Post-exchange)	10.6	...	Partial + at 6 min.	.....	Pink, peaceful, asleep	Penicillin SR 1 cc. Dierysticin 1 cc.	25 mg. q. 12 h.
7/18	10.4	...	.....	.....	Apparent good health	Penicillin SR 1 cc. Dierysticin 1 cc.	25 mg. q. 12 h.
7/20	10.3	1.0	.....	Moderate erythroid hyperplasia	Mild thrombophlebitis; cleared rapidly	Penicillin SR 1 cc. Dierysticin 1 cc.	.....
7/21	10.6	...	.....	.....	Good health	Penicillin SR 1 cc. Dierysticin 1 cc.	.....
7/22	10.7	6.0	.....	.....	Good health	Penicillin SR 1 cc. Dierysticin 1 cc.	.....
7/23	10.7	8.0	+ in 2 min.	.....	Good health	Penicillin SR 1 cc. Dierysticin 1 cc.	.....
7/24	11.2	10.0	.....	.....	Good health	Penicillin SR 1 cc. Dierysticin 1 cc.	.....
7/27	10.6	2.5	.....	.....	Good health	Penicillin SR 1 cc. daily	.....
7/28	10.5	3	.....	.....	Good health	Penicillin SR 1 cc. daily	.....
7/29	10.8	2	+ in 2 min.	.....	Good health	Penicillin SR 1 cc. daily	.....
8/4	13.2	6.4	.....	.....	Good health	Oral penicillin 150,000 units b.i.d.	.....
8/10	12.3	5.2	.....	.....	Good health	Oral penicillin 150,000 units b.i.d.	.....
8/17	12.0	5.0	.....	.....	Good health	Oral penicillin 150,000 units b.i.d.	.....
8/31	10.0	7.2	.....	.....	Good health	Oral penicillin 150,000 units b.i.d.	.....
9/3	10.0	8.4	.....	.....	Good health	Oral penicillin 150,000 units b.i.d.	.....
9/7	8.9	12.5	.....	.....	Good health	Oral penicillin 150,000 units b.i.d.	.....
9/26	9.4	9	.....	.....	Sibling had scleral icterus	Oral penicillin 150,000 units b.i.d.	.....
9/28	9.8	7.4	.....	.....	Apparent good health	Oral penicillin 150,000 units b.i.d.	.....
10/5	9.6	7.6	.....	.....	Becoming jaundiced	Oral penicillin 150,000 units b.i.d.	.....
10/9	8.8	12.3	.....	.....	Increasing jaundice	Oral penicillin 150,000 units b.i.d.	.....
10/13	6.5	...	.....	.....	Admitted jaundiced	Oral penicillin 150,000 units b.i.d.	.....
10/14	6.6	8.4	+ in 1 min.	.....	Liver and spleen large; ears normal	Oral penicillin 150,000 units b.i.d.	.....

ing cortisone. Ascites was evident on the fourth day, but disappeared when the cortisone dosage was reduced. She was discharged on Nov. 1, eleven days after the beginning of cortisone therapy, her hemoglobin having risen from 6.3 to 13 gm. (Nov. 7). Her liver and spleen were still large, and her Coombs test still positive within one minute.

Since that time she has been in good health. Her hemoglobin levels have remained between 13 and 14 gm. There is no reticulocytosis. Cortisone tests with the eluate and with the serum antibody present in July, 1953, are being done in an attempt to determine whether this antibody is specific against any blood-group antigen. At present it appears to be a nonspecific panhemagglutinin.

TABLE 3.—*Course of Disease from Second Admission until March 16, 1954*

Date	HGB., Gm./ 100 Cc.	Reticulocytes	Coombs	Serum Bilirubin	Clinical Condition	Antibiotics	Cortisone
10/14	6.6	8.4	+ 1 min.	5.75 direct 7.5 total	Jaundiced, liver and spleen large; ears normal	.....	.....
10/15	...	13.4	.....	.....	.....	.....	.....
10/16	Spherocytes	7.2	.....	.....	.....	.....	.....
10/19	6.3	14.0	.....	.....	.....	.....	.....
10/20	...	...	.....	.....	.....	Penicillin SR 1 cc. e.o.d.	.....
10/21	...	...	.....	.....	.....	.....	50 mg. q. 6 h. daily
10/22	7.9	14.4	.....	8 direct 22 total	Deep jaundice	Penicillin SR 1 cc. e.o.d.	50 mg. q. 6 h. daily
10/23	...	...	.....	.....	.....	.....	50 mg. q. 6 h. daily
10/24	...	13.6	.....	.....	.....	Penicillin SR 1 cc. e.o.d.	50 mg. q. 6 h. daily
10/27	10.6	13.3	.....	0.35 direct 5.75 total	Ascites present; jaundice fading	.....	50 mg. q. 6 h. daily
10/28	...	...	.....	.....	.....	Penicillin SR 1 cc. e.o.d.	50 mg. t.i.d.
10/29	...	...	+ 1 min.	.....	Liver and spleen large; no jaundice	Penicillin SR 1 cc. e.o.d.	50 mg. t.i.d.
10/30	...	6.6	.....	.....	Ascites gone	Penicillin SR 1 cc. e.o.d.	50 mg. b.i.d.
11/7	13.0	5.2	.....	.....	.....	Oral penicillin 150,000 units b.i.d. daily	25 mg. b.i.d.
11/12	14.6	...	.....	.....	Appears normal; liver and spleen large	Oral penicillin daily	25 mg. b.i.d.
11/27	12.5	1.8	.....	.....	.....	Oral penicillin daily	25 mg. b.i.d.
12/11	15.0	1.0	.....	.....	.....	Oral penicillin daily	25 mg. daily
12/16	13.2	1.3	.....	.....	.....	Oral penicillin daily	25 mg. daily
1/27	13.6	1.6	+ in 2 min. indirect —	.....	Normal	Oral penicillin daily	25 mg. daily
2/15	13.4	2.5	.....	.....	Spleen and liver not palpable	Oral penicillin daily	25 mg. daily
3/1	13.0	3.5	.....	.....	.....	Oral penicillin daily	25 mg. daily
3/16	14.0	2.5	.....	.....	.....	Oral penicillin daily	25 mg. daily

COMMENT

We are in no position to say just what the cause of the acquired hemolytic disease is in this child. However, its presence for about one year before her first admission and apparent exacerbation with each upper respiratory infection and also the recurrent running ear suggest periods of autoantibody formation stimulated by a specific virus or by various infectious agents.

Moolten and Clark [1] reported the isolation of the virus of Newcastle disease from the red cells of a patient with acute acquired hemolytic anemia and have also reported

has been continued in gradually diminishing amounts. She is now (April 1, 1954) receiving 25 mg. by mouth daily. Oral penicillin is being given prophylactically to prevent recurrence of the ear infection. When she was last examined, Jan. 27, 1954, her spleen and liver were no longer palpable and she appeared a normal healthy little girl. Her direct Coombs test was positive in two minutes, but at this time no free antibody could be demonstrated in her serum as evidenced by a negative indirect Coombs test. Eluates from her erythrocytes Jan. 27 showed moderate hemagglutinating activity against all cells tested. Further

finding viruses in association with hemagglutinative and hemolytic syndromes complicating Hodgkin's disease, leukemia, lymphosarcoma, and other reticuloendothelial disorders. Morgan,[2] on the other hand, was unable to isolate any virus from the erythrocytes of six patients and the spleens of three others with acquired hemolytic anemia. We have no direct proof that viral, or any other infection is the cause of autoantibody production in our patient.

Our experience with this child demonstrates the problems inherent in the treatment of acquired hemolytic anemia. The initial lack of response to a four and one-half day course of corticotropin and cortisone, when cortisone was so successful in October, is difficult to explain. Improvement was observed in October within three days of the start of treatment. In July her anemia and degree of hemolysis were severer, she had a purulent ear infection, and she was given two transfusions of incompatible blood. Some combination of these factors may have been responsible for causing the sudden depression of marrow function, as noted July 16, and may have been instrumental in preventing the expected improvement with corticotropin and cortisone.

Transfusions were urgently required because of her severe anemia. However, they appeared to accelerate the hemolysis; transfusion reactions developed, and she almost died. Wiener, Samwick, Morrison, and Loewe [3] have recorded the history of a similar patient, a 47-year-old woman with severe acquired hemolytic anemia, made worse by apparently compatible blood transfusion, who died of continuing hemolysis and anemia 24 hours after corticotropin therapy was begun. This patient would possibly have benefitted from a replacement transfusion. It might have saved her life, as it did that of our patient. It would at least have delayed her death and have given the corticotropin more time to take effect.

The gratifying, albeit temporary, remission which we observed following replacement transfusion has been reported by others in adults (Piney [4]; Cattan and co-workers [5]; Milliez and co-workers [6]). The beneficial effect is perhaps due to (1) removal of a large amount of antibody both free and attached to red cells, and (2) provision of a large volume of fresh red cells to absorb and further dilute the antibody. That replacement transfusion did not alter the fundamental course of the disease is shown by the rapid increase in strength of the direct Coombs test in the subsequent two weeks. Thus the donor red cells became "coated" in the same manner as her own cells. However, at time of discharge July 30, the Coombs test was positive at the end of two minutes, a lower degree of activity than at the time of her admission. Just as her improvement following replacement transfusion lies in the reduced amount of autoantibody present, the explanation for her decline during late September and early October is the increase in autoantibody as evidenced at that time by a Coombs test positive in less than one minute.

Her apparently complete remission following the use of cortisone may be for the same reason. The cortisone, although it may have acted initially by in some way interrupting the interaction of antigen and antibody, also appears to have reduced the amount of antibody produced. There is now no demonstrable free circulating antibody; her indirect Coombs test is negative, and the direct Coombs test is just positive at two minutes. Gardner and co-workers,[7] in similar cases treated with corticotropin, observed a sharp drop in Coombs titer, which persisted only as long as the drug was administered. Davidson and co-workers [8] saw complete remission and reversion of the direct Coombs test to negative on 100 mg. corticotropin daily.

Not all patients respond to cortisone or to splenectomy in the same fashion. Many failures to improve and exacerbations of hemolysis have been observed following splenectomy (Dameshek and Rosenthal [9], Young and co-workers,[10] Saint and Gardner [11]). Similarly, failure to respond to corticotropin and cortisone or relapse during or after stopping therapy are reported (Dame-

shek and co-workers,[12] Sacks and co-workers,[13] Gunz and Aiken[14]). For this reason some authors favor initial preparation with cortisone and then splenectomy; whereas others use cortisone, resorting to splenectomy only if drugs fail to control the disease. Because of our child's sustained improvement while on cortisone, we are not considering splenectomy at the present time.

CONCLUSIONS

Replacement transfusion has no curative effect in acquired hemolytic anemia. However, in the face of severe hemolysis accelerated after simple transfusions it may be lifesaving, allowing time for corticotropin or cortisone to take effect or making splenectomy possible.

SUMMARY

A patient with idiopathic acquired hemolytic anemia made worse by simple transfusions and initially unresponsive to corticotropin and cortisone, had an excellent temporary response following a replacement transfusion of two liters of blood. Relapse occurred two months later. She then had a complete remission on cortisone, which has continued now for five months. She is receiving a daily maintenance dose of cortisone. Replacement transfusion is suggested as a means of tiding the patient over a crisis and allowing time for more specific treatment to be instituted.

Dr. H. Medovy gave permission to publish the history of this patient, and Dr. Bruce Chown, Professor of Pediatrics, University of Manitoba Faculty of Medicine, and Director of the Blood Group Research Laboratory, gave advice and criticism.

REFERENCES

1. Moolten, S. E., and Clark, E.: Viremia in Acute Hemolytic Anemia and in Autohemagglutination: Report of Case and Review of Literature, with Special Reference to Virus of Newcastle Disease, A. M. A. Arch. Int. Med. **89**:270 (Feb.) 1952.

2. Morgan, H. R.: Acquired Hemolytic Anemia and Viremia, J Lab. & Clin. Med. **40**:924 (Dec.) 1952.

3. Wiener, A. S.; Samwick, A. A.; Morrison, M., and Loewe, L.: Acquired Hemolytic Anemia, Am. J. Clin. Path. **22**:301 (April) 1952.

4. Piney, A.: Acquired Hæmolytic Anæmia, Sang **21**:229, 1950.

5. Cattan, R.; Frumusan, P.; Dausset, J., and Trelat, R.: Ictère hémolitique acquis traité notamment par deux exsanguino-transfusions: Persistance des stigmates biologiques; Stabilisation clinique, Bull. et mém. Soc. méd. hôp. Paris, **67**:45 (Jan. 12-19) 1951.

6. Milliez, P.; Laroche, C.; Dubost, C.; Drefus, B.; Dausset, J., and Moreau, L.: Maladie neurohémolytique apparemment acquise: Présence d'anticorps circulants du type incomplet; Influence des exsanguino-transfusions; Remarquables résultats de la splénectomie sur l'hémolyse et sur les troubles neurologiques, Bull. et mém. Soc. méd. hôp. Paris **67**:771, (May 18-25) 1951.

7. Gardner, F. H.; McElfresh, A. E.; Harris, J. W., and Diamond, L. K.: The Effect of Adrenocorticotrophic Hormone (ACTH) in Idiopathic Acquired Hemolytic Anemia as Related to the Hemolytic Mechanisms, J. Lab. & Clin. Med. **37**: 444 (March) 1951.

8. Davidson, L. S. P.; Duthie, J. J. R.; Girdwood, R. H., and Sinclair, R. J. G.: Clinical Trials of A.C.T.H. in Hæmolytic Anæmia, Brit. M. J. **1**:657 (March 31) 1951.

9. Dameshek, W., and Rosenthal, M. C.: Symposium on Specific Methods of Treatment: The Treatment of Acquired Hemolytic Anemia, with note on Relationship of Periarteritis Nodosa to Hemolytic Anemia, M. Clin. North America **35**:1423 (Sept.) 1951.

10. Young, L. E.; Christian, R. M., and Izzo, M. J.: Some Newer Concepts of "Congenital" and "Acquired" Hemolytic Anemias, M. Clin. North America **35**:571 (March) 1951.

11. Saint, E. G., and Gardner, H. J.: The Successful Treatment of Severe Acquired Hæmolytic Anæmia with Adrenocorticotropic Hormone (ACTH), M. J. Australia **2**:305 (Aug. 30) 1952.

12. Dameshek, W.; Rosenthal, M. C., and Schwartz, L. I.: The Treatment of Acquired Hemolytic Anemia with Adenocorticotrophic Hormone (ACTH), New England J. Med. **244**:117 (Jan. 25) 1951.

13. Sacks, M. S.; Workman, J. B., and Jahn, E. F.: Diagnosis and Treatment of Acquired Hemolytic Anemia, J. A. M. A. **150**:1556 (Dec. 20) 1952.

14. Gunz, F. W., and Aiken, M. H.: Treatment of Acquired Hemolytic Anemia By Means of ACTH, New Zealand M. J. **51**:283 (Oct.) 1952.

ARTHROGRYPOSIS MULTIPLEX CONGENITA IN IDENTICAL TWINS

EARLE L. LIPTON, M.D., Syracuse, N. Y.
and
SYDNEY H. MORGENSTERN, M.D., Chicago

IDENTICAL twins afflicted with arthrogryposis multiplex congenita have never before been described in medical literature to our knowledge. In an excellent review article in 1951, James [1] stated that two cases had never been reported in the same family. A recent report cited two sets of probably authentic identical twins, each of which consisted of one normal and one affected infant.[2] On the basis of such observations, much speculation as to the etiology has been presented in the past. The knowledge that arthrogryposis multiplex congenita can occur in identical twins is therefore of importance and will be briefly discussed as it relates to etiologic considerations.

REPORT OF A CASE

Twin girls were born to a multiparous mother on Dec. 29, 1952, terminating an uncomplicated pregnancy. The first infant (R. E. R.) was delivered at 10:25 a. m. after a cephalic presentation. She weighed 2700 gm. and was normal except for the orthopedic deformities described below.

The second infant (R. H. R.) was delivered after a footling breech presentation three minutes later. She weighed 2760 gm. and manifested anomalies identical to those of her sister.

Three previous siblings in this family of Mexican origin are living and well at ages 7, 3½, and 2½ years. The first child born to this mother died at five months of age as a result of pneumonia. No family history of talipes equinovarus or any other congenital orthopedic defect was obtained after repeated questioning. Two sisters of the father died of tuberculosis in adolescence, and a younger brother was said to have died from post-tonsillectomy hemorrhage.

The twins were under the care of a private physician until three months of age, when, on March 27, 1953, they were seen at the Research and and Educational Hospitals, University of Illinois. The findings were unchanged from those noted at birth except that physical signs of bronchopneumonia were found which subsequently responded to antibiotic therapy in both infants.

The general appearance of the twins was identical and was thought by all observers to correspond entirely with previously described cases of arthrogryposis multiplex congenita (Fig. 1). The hair was black and the eyes were dark brown. Each

Fig. 1.—*A*, R. E. R. *B*, R. H. R.

child manifested bilateral talipes equinovarus of the same severity (Fig. 2) and bilateral adduction contractures of the metacarpal-phalangeal joints of the thumbs, so that these digits were pressed against the palms of the hands (Fig. 3). Stiffness of all of the larger joints of the upper and lower extremities prevented normal flexion or extension. The remainder of the physical examination was negative.

Subsequent application of orthopedic casts and manipulation, at Cook County Hospital, resulted in some improvement in these articular rigidities. R. H. R. later showed evidence of developmental retardation and died of bronchopneumonia at 15 months of age. Permission for postmortem examination could not be obtained.

Present addresses: State University of New York at Syracuse College of Medicine, Department of Pediatrics (Dr. Lipton); Cook County Hospital, Department of Orthopedics (Dr. Morgenstern).

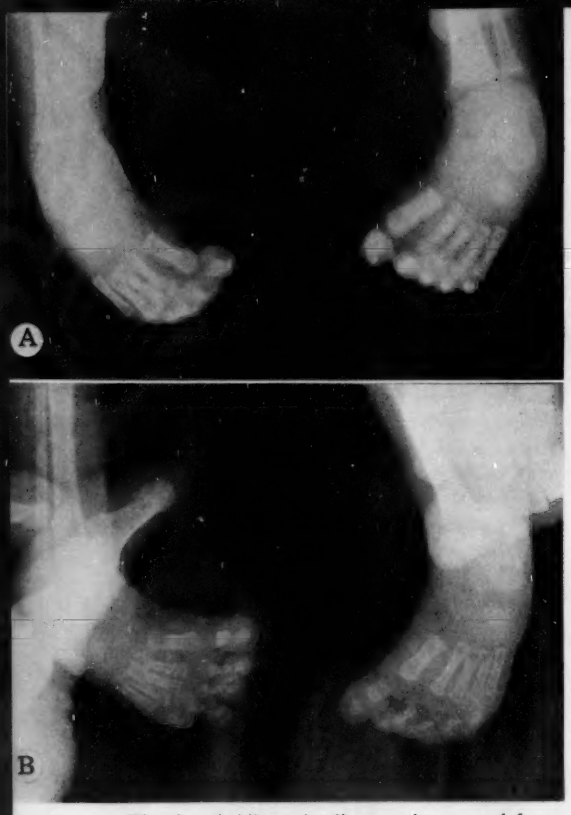


Fig. 2.—*A*, bilateral talipes equinovarus deformity of R. E. R. *B*, R. H. R., identical deformity.

LABORATORY FINDINGS

The blood formulas of the twins were identical: A_1 MNs cDEe (Rh_2) P Fy^a kk.*

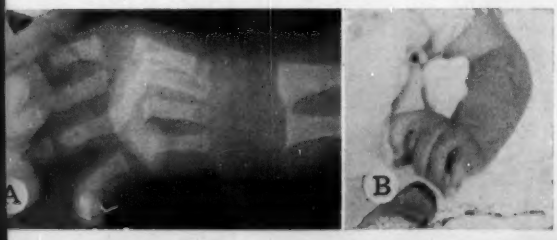
The placenta consisted of a double fused specimen, measuring 23 cm. × 21 cm. × 3.0 cm. The cotyledons were completely represented, and there was no apparent deficiency of the fetal membranes. One umbilical cord, of 24 cm. length, was eccentrically attached to its corresponding portion of the placenta. The other measured 27.5 cm. and was marginally attached. Each showed several varicosities. Careful dissection demonstrated separate amnions but a single common chorion.

Histologic examination revealed a normal placenta in the late stages of development. All its features were consistent with the diamniotic-monochorionic double fused placenta of identical twins.[3]

Roentgenograms demonstrated the abnormal osseous relationships seen clinically (Figs. 2 and 3). There appeared to be a subluxation of the metacarpal-phalangeal joint of all of the thumbs. No hip abnormality was noted. The bone age appeared somewhat retarded. The remainder of the laboratory tests were noncontributory.

* Davidson, I.: Personal communication to the author.

Fig. 3.—*A*, hand of R. H. R., demonstrating adduction deformity of thumb. *B*, typical position of the hands of both twins, with thumb projecting between index and second digits.



COMMENT

The identical blood formulas, physical characteristics—including ear configuration—and monochorionic placenta leave little doubt that the twins described in this report are monozygotic. Several previous reports did not identify the twins as monozygotic or dizygotic.† Two sets of twins were almost certainly identical,[2] while another reported set was definitely dizygotic.[6]

The occurrence of the disease in but one of double-ovum twins[6] suggests a genetic basis, as pointed out by James,[1] but it is possible that noxious agents of many types may alter the early development of but one of the growing fetuses in utero. Though apparently not noted in past reports,[1] Buchanan has cited a case in which the disease occurred in three successive generations.[7] He also observed cases in siblings.

The lack of frequent familial occurrence in past reports does not exclude a genetic etiology. Chance combinations of multiple genes, mutations resulting from position effect and unequal crossing over of genes, and a variety of other mechanisms might explain this. Furthermore, severely afflicted persons have probably rarely procreated in the past. Buchanan's cases in successive generations have not been described in detail, and thus one cannot ascertain whether a dominant mode of inheritance was responsible. His observations and the present case strongly suggest a hereditary basis for at least some of the patients with this disease.

Studies of the nature of the pathological process have not further clarified the problem of etiology. Some investigators have stated that the disease in man and an analogous condition in sheep are due to muscle degeneration unrelated to central-nervous-system disease.‡ Through selective breeding, the homozygous state of an autosomal recessive factor can be produced in the sheep.

† References 4 and 5.

‡ References 4, 8, and 9.

The sheep are stillborn or die shortly after birth, in contradistinction to the human disease.

Other authors described degenerative changes in the spinal cord, resembling the infantile myelopathies, and suggested that the clinical picture depends on the time when the peripheral neurones are affected.§ Those cases may truly represent primary central-nervous-system disease of various types. Buchanan [12] has also remarked on the association of amyotonia congenita with universal shortening of all the flexor tendons at birth to give the syndrome of arthrogryposis. Absence of the reaction of degeneration in some cases electromyographically tested, the absence of neuronal or cord disease in other pathologic studies, and the lack of progression of the process postnatally indicate that this pathogenesis probably cannot be generalized to include all cases.

Many authors in the past have cited the intrauterine compression hypothesis. The unusual simultaneous occurrence of oligohydramnios or hyperhydramnios or multiple births does not seem consistent with this. The identical lesions in our twins make such a theory untenable in this particular case. The total absence of lesions in the normal twin of previous sets would also be difficult to explain if excessive intrauterine compression were the principal etiologic factor.

Badgely [13] stated that the entity could represent an embryonic malformation due to arrested development in or before the third month of fetal life. A primary pathological change of the muscles at that stage would prevent them from producing the normal characteristic rotation of the human limb buds. James [1] also concluded that the disease is the result of an embryonic mesenchymal dysplasia in the first two intrauterine months.

These theories are consistent with the recent reviews and studies by Warkany,[14] Ingalls,[15] and others. There seems little doubt that mesenchymal tissue destined to become the muscle, tendon, cartilage, and bone components of certain joints could be adversely affected by various noxious agents in the early phases of development. It is known experimentally that a relatively simple embryologic anomaly can set up a chain of abnormal reactions resulting in far-reaching and seemingly unrelated effects.[14]

It is possible that the identical twins were similarly afflicted because of their simultaneous development. Dizygotic twins might conceivably be at somewhat different stages when the injury occurs, depending upon their individual inherent patterns of development. Hillman and Johnson's cases of nonaffected identical twins argue against this point, as does the fact that no other normal dizygotic twin suffered from any type of anomaly.

However, as stated before, it is conceivable that only one twin, whether dizygotic or monozygotic, might be affected by intrauterine trauma. That environmental factors can enhance the variable expressivity or penetrance of a genetic trait has been shown experimentally.[14] One might expect that anoxia could enhance the process in one of a set of monozygotic twins. It is interesting that one of Hillman and Johnson's affected twins (Case 1) was almost 1 kg. lighter than his normal brother. The greatest difference observed by Potter [8] in living twins was 995 gm. Occasional greater differences were noted by Ahlfeld, as cited by Stander.[16] Unequal nutrition resulting from the distribution and size of the intercommunicating placental vessels is sometimes the apparent cause of extreme underdevelopment of one twin, often resulting in death. Though the evidence is meager, one might infer that the affected identical twin was adversely influenced in utero while the same genetic factors in the other twin were not similarly enhanced by intrauterine trauma. Thus the identical hereditary pattern was not given clinical expression in the nonaffected twin.

It must be concluded that this perplexing problem cannot be answered with our present information. It is likely that this disorder can result from genetic factors or/and aberrant intrauterine development related to a variety of noxious agents affecting mesen-

§ References 10 and 11.

chymal and possibly ectodermal tissue in the first trimester of pregnancy. The timing of the injury as related to the state of development of the tissue involved may be of greatest importance. These facts, together with the observation that "hereditary forms can be simulated by nonhereditary phenocopies," [14] indicate the complexity of the problem.

SUMMARY

Monozygotic twins identically afflicted with arthrogryposis multiplex congenita are described. This represents the first such report noted in available medical literature.

It is concluded that classic recessive or mutational genetic factors [17] may be responsible for many of the cases. Early intrauterine injury to mesenchymal and/or ectodermal tissue, possibly acting in a synergistic fashion with basic genetic defects which would otherwise not be decisive, could account for all other cases.

Dr. Julius B. Richmond, Head of the Department of Pediatrics, and Dr. Lytt I. Gardner, Associate Professor of Pediatrics, at the State University of New York at Syracuse College of Medicine, gave helpful comments during the preparation of this paper.

Dr. Morris Goldberg, pathologist at the South Chicago Community Hospital, gave permission for use of the report of his study of the placenta.

REFERENCES

1. James, T.: Multiple Congenital Articular Rigidities: A Review of the Literature with Reports of 2 Cases, Edinburgh M. J. **58**:565, 1951.

2. Hillman, J. W., and Johnson, J. T. H.: Arthrogryposis Multiplex Congenita in Twins, J. Bone & Joint Surg. **34-A**:211, 1952.

3. Potter, E. L.: Pathology of the Fetus and the Newborn, Chicago, Year Book Publishers, Inc., 1952, pp. 175-176.

4. Howard, R.: A Case of Congenital Defect of the Muscular System (Dystrophia Muscularis Congenita) and its Association with Congenital Talipes Equino-Varus, Proc. Roy. Soc. Med. **1**: 157, 1907-1908.

5. Bearán, M. S.: Arthrogryposis, Cir. ap. locom. **5**:352, 1948.

6. Oleaga, F., and Muguruza, J.: Arthromyodysplastic syndrome in Twin with Normal Brother: Study of Congenital Arthrogryposis, Rev. españ. pediat. **6**:835, 1950.

7. Buchanan, D., in Grulee, C. G., and Eley, R. C.: The Child in Health and Disease: A Textbook for Students and Practitioners of Medicine, Baltimore, Williams & Wilkins Company, 1952, Chap. 77.

8. Roberts, J. A. F.: The Inheritance of a Lethal Muscle Contracture in the Sheep, J. Genetics **21**:57, 1929.

9. Middleton, D. S.: Studies on Prenatal Lesions of Striated Muscle as a Cause of Congenital Deformity: Congenital Tibial Kyphosis; Congenital High Shoulder, Myodystrophia Fœtalis Deformous, Edinburgh M. J. **41**:401, 1934.

10. Price, D. S.: A Case of Amyoplasia Congenita, with Pathological Report, Arch. Dis. Childhood **8**:343, 1933.

11. Brandt, S.: A Case of Arthrogryposis Multiplex Congenita Anatomically Appearing as Fœtal Spinal Muscular Atrophy, Acta pædiat. **34**:365, 1947.

12. Buchanan, D.: Symposium on Pediatrics: Some Disorders of the Motor Unit in Infancy and Childhood, M. Clin. North America **34**:147, 1950.

13. Badgely, C. E.: Correlation of Clinical and Anatomical Facts Leading to a Conception of the Etiology of Congenital Hip Dysplasia, President's Address, J. Bone & Joint Surg. **24**:503, 1943.

14. Warkany, J.: Etiology of Congenital Malfomation, in Levine, S. Z.; Butler, A. M.; Holt, L. E., Jr., and Weech, A. A., Editors: Advances in Pediatrics, Chicago, Yearbook Publishers, Inc., 1947, Vol. 2.

15. Ingalls, T., in Levine, S. Z.; Anderson, J. A.; Dann, M.; Holt, L. E., Jr.; Weech, A. A., and Wegman, M. E., Editors: Advances in Pediatrics, Chicago, Yearbook Publishers, Inc., 1953, Vol. 6.

16. Stander, H. J.: Textbook of Obstetrics Designed for the Use of Students and Practitioners, Ed. 9, New York, Appleton-Century-Crofts, Inc., 1945.

17. Genetic Patterns in Correspondence, Retinoblastoma, Brit. M. J. **2**:591, 1954.

PROLONGED SEPTIC LEPTOSPIROSIS

A New Species?

HARRY J. LAWLER, M.D., Billings, Mont.

LEPTOSPIRA infections, several varieties of which occur in the United States (caused by L. icterohemorrhagiae, L. canicola, L. pomona, L. autumnalis, and L. grippotyphosa) produce many syndromes. Classic Weil's disease, icteric and anicteric, is well known as a result of both L. icterohemorrhagiae and L. canicola infection. Both may also produce aseptic meningitis, hemorrhagic nephritis, or iridocyclitis. L. pomona is reported more likely to produce iridocyclitis and aseptic meningitis. L. autumnalis causes "pretibial fever," named for the pretibial erythema commonly seen. L. grippotyphosa produces a myalgic febrile syndrome without icterus, frequently with meningeal signs. In each case accurate diagnosis depends not on clinical syndromes but on a specific agglutination test. For a recent brief summary of the leptospiroses, with key references, the reader is referred to that of Jeghers.[1]

The following case is reported here because it is unlike any found in the literature and seems unique. It is the first reported case of any of the leptospiroses from the state of Montana, according to the records of the State Board of Health.

N. R., a 9-year-old white girl, was admitted to St. Vincent Hospital on April 6, 1953. She had been ill for a day, with high temperature, sore throat, vomiting, watery brown diarrhea, and painfully stiff back and extremities. Initial examination showed a slim fairly well-developed girl lying rigidly, resenting movement, and complaining of pain in most of her muscles, joints, and abdomen. Rectal temperature was 104.8 F; blood pressure, 100/64. The feet were held in a firm "foot-drop" position; dorsiflexion produced intense pain in the calf muscles. These muscles, especially, but all major groups to some extent, were tender to palpation. The joints were not swollen or tender. There was an irregular "butterfly" erythema of the nose and adjacent cheeks and over the extensor surfaces of the major joints; this erythema was prominent during hyperpyrexia throughout the illness, but tended to disappear when the temperature would drop, briefly, to normal. There were perhaps a hundred tiny petechiae scattered over all aspects of the trunk and extremities. The pupils responded to light and were equal; jaundice and conjunctivitis remained absent for the entire illness. There was a mild inflammation of the small tonsils and pharynx; a thin gray mucoid postnasal drip was present. The lungs were clear. The heart sounds, though rapid, were of good quality; no murmurs were heard. There was a mild generalized abdominal tenderness. The liver was felt at the costal margin throughout the illness and was never tender. The spleen was not felt and never became enlarged or tender. The neck and back were stiff.

Cultures of blood, spinal fluid, urine, and stool were obtained before therapy; the first three were sterile, and the latter was negative for bacterial or parasitic pathogens. Spinal fluid was water clear and contained no cells. Urine was normal. Initial white blood cell count was 26,600, with segmented neutrophiles, 81%; band forms, 8%; lymphocytes, 9%; monocytes, 10%; toxic granulation was noted. Hemoglobin was 12 gm. per 100 cc.; red cell count was 4,500,000.

On a presumptive diagnosis of sepsis, initial therapy was with an intravenous drip of 3.5 gm. of sodium sulfadiazine in M/6 sodium lactate solution; 400,000 units of penicillin procaine, with 0.5 gm. of streptomycin, was given intramuscularly twice daily. The sulfonamide therapy was continued orally with a mixture of sulfadiazine and sulfamerazine, 1.5 gm. every six hours. Acetylsalicylic acid, sponge baths, ice bags, cold water enemas, wet sheeting, and oxygen tent were used to combat the episodes of extreme hyperpyrexia. Fortunately, clear liquids were retained. There seemed to be an initial response to therapy; the temperature dropped to 100 F, axillary, the second day, and the diarrhea ceased; no new rash appeared, and the petechiae faded out

over the next three days. The muscle pain continued unabated. A moderate and slowly progressive enlargement of all palpable lymph nodes began; those in the axillae were to enlarge to 2 to 3 cm. in diameter during the next few days.

Septic temperature recurred on the third day and continued for two months, with peaks in the 104 to 106 F range despite most vigorous efforts to combat them. With nothing but negative results returning from the laboratory, further diagnostic efforts were made; an endocarditis was seriously considered (possibly on a bicuspid aortic valve, in the complete absence of any clue to congenital or acquired heart disease); repeated blood cultures on penicillinase media continued negative. An electrocardiogram, April 9, showed low voltage QRS in Lead I, elevated ST in Leads II and III and aV_F, normal V leads. Serially improved electrocardiograms were recorded on April 14 and 23. Chest x-ray for cardiac size was normal April 11, but on April 21 there was a moderate generalized enlargement of the cardiac silhouette. It was concluded that there was evidence of a myocarditis, probably toxic, entirely compatible with the septic disease process but suggestive of no specific disease. The lung fields remained normal.

With failure of initial antibiotic therapy, penicillin procaine was increased to 3,200,000 units daily for two days, then 7,000,000 units daily for five days, with 1.5 gm. of probenecid daily to block renal penicillin excretion. Simultaneously, 2 gm. of streptomycin and 1.5 gm. of chlortetracycline (Aureomycin) were given daily. No benefit occurred. The muscle pain and tenderness continued, and the generalized lymphadenopathy became more noticeable; vigorous antipyresis remained necessary. On April 15, these antibiotics were discontinued, and 1.5 gm. of erythromycin and 1.5 gm. of chloramphenicol were given daily for five days. When this proved worthless, 3 gm. of oxytetracycline daily was added to the chloramphenicol for four more days. This massive therapy proving unavailing, all antibiotics were discontinued. For the next two and one-half months the mainstay of therapy was nutritional and supportive nursing care. A high-protein diet, with supplemental vitamins and iron, was well taken. Three times she developed a secondary anemia and received a transfusion.

The leucocytosis continued, reaching a peak of 70,000, with 70% band forms, on April 16; a decline over the next 10 days to 5,850 was followed by a prompt rise, reaching another peak of 33,000 on May 15. Toxic granulation and a definite left shift in the differential count were always found. The platelet count remained normal.

With the splendid consultative aid of Dr. John Hurly and Dr. Robert Blomberg, internists, efforts to solve the diagnostic problem were continued. Cultures and agglutinations for typhoid, paratyphoid, Brucella, Pasteurella tularensis, and the various strains of Proteus were repeatedly negative. Heterophile antibody was twice absent. Histoplasma and malarial parasites were absent from smear and culture of blood and marrow. Cephalin-cholesterol flocculation tests were negative. Urine cultures were negative. A calf-muscle biopsy showed no evidence of trichinae, arteritis, or myositis. The sternal marrow showed "extreme hyperplasia of the granulocytic element; most of the cells are promyelocytes or myelocytes . . . the bone marrow does not represent leukemia, but is evidence of bone marrow stimulation to infectious stimuli" (Dr. Mary Martin, pathologist).

The diagnosis was finally suggested by the results of the agglutination tests for leptospirae, done at the U. S. Public Health Service Laboratory, Hamilton, Mont. Blood drawn the 19th day of the illness contained a 1:100 titer against L. icterohemorrhagiae; it was negative with other species of Leptospira (canicola, pomona, autumnalis, grippotyphosa, bataviae, and hebdomadis). On the 35th day of the disease, the titer (described as partial) had risen to 1:10,000 against L. icterohemorrhagiae; again, no reaction was obtained with the other species. It was concluded that antibodies for Leptospira were present but that the titer obtained represented a cross reaction with another, as yet unknown, species. Such cross reactions with L. icterohemorrhagiae are well recognized among the leptospirae. A third sample, on the 66th day of the illness, showed no titer for any leptospirae; this disappearance with convalescence was interpreted again as consistent with an infection with an unknown species of Leptospira. Three months after the end of the illness, blood was sent to Dr. J. W. Wolff, the Institute for Tropical Hygiene, Amsterdam, Netherlands; it was negative for reaction with any species of Leptospira tested (including the ones tested here and, in addition, sejroe, ballum, hyos, pyrogenes, australia A, medanensis, javanica, naami and mankarso).

Efforts to recover an organism were unsuccessful, probably because we were not supplied with young guinea pigs or other test animals early in the disease. Two older ones were inoculated with blood in the third week; both remained healthy, and cultures of their blood were negative. Three more, less than 6 weeks of age, were inoculated with blood drawn the 34th day of the illness and sent to the Hamilton laboratory; no organism was recovered.

Our patient finally made a complete recovery after three months of fever; the lysis of the septic temperatures consumed an entire month. Coincidentally, she gained weight from a low of 48 lb. (21.8 kg.) to 60½ lb. (27.4 kg.) three and one-half months after the start of the illness. The erythema and itching disappeared with the fever. Her hair, gradually lost during the worst of the illness, regenerated by the

seventh month afterward. The enlarged lymph nodes very slowly returned to normal by the 12th month. No iridocyclitis developed. A year later she was making normal progress in school and in play.

SUMMARY

A case of prolonged septic anicteric leptospirosis in a 9-year-old girl is reported. Initially it was characterized by fever, sore throat, diarrhea and vomiting, intense myalgia, petechiae, extensor and facial erythema, meningismus, and leucocytosis. Septic fever continued for two months, during which time myalgia, generalized lymphadenopathy without hepatomegaly or splenomegaly, toxic myocarditis, pruritus, loss of hair, hyperleucocytosis (up to 70,000), and secondary anemia were prominent. No response to massive and multiple antibiotic therapy occurred. Defervescence was by lysis, during an entire month. Serological tests suggested that the cause was a Leptospira infection, possibly a new species.

REFERENCE

1. Jeghers, H.: The Leptospiroses in the United States, Bull. New England M. Cent. **15**:61-71 (June) 1953.

News and Comment

ANNOUNCEMENTS

Symposium on Antimetabolites.—The National Vitamin Foundation will present a symposium on the Antimetabolites—Their Modes of Action and Therapeutic Implications, on Tuesday, March 1, 1955, at The Biltmore, Madison Ave. at 43d St., New York. This is to be held in conjunction with the Tenth Annual Meeting of the National Vitamin Foundation.

The chairman of the morning session is to be Dr. Paul L. Day. The contributions for this session are as follows:

Dr. Edwin L. Hove, "Anti-Vitamin E Stress Factors as Related to Fatty Peroxides"

Dr. L. R. Cerecedo, "Thiamine Antagonists"

Dr. Karl Paul Link, "Vitamin K and the 4-Hydroxycoumarin Anticoagulants"

Dr. Joseph H. Burchenal, "Folic Acid Antagonists"

The chairman of the afternoon session is to be Dr. Robert W. Heinle. The contributions for this session are as follows:

Dr. George H. Hitchings, "Purine and Pyrimidine Antagonists"

Dr. D. W. Woolley, "A Naturally Occurring Antimetabolite of Methionine in the Causation of a Disease"

Dr. O. D. Bird, "Pantothenic Acid Antagonists"

Dr. Wayne W. Umbreit, "Vitamin B_6 Antagonists"

Dr. John P. Lambooy, "Riboflavin Antagonists"

All persons attending the symposium are requested to register. A registration fee will not be charged. Proceedings will be published and available through the National Vitamin Foundation, Incorporated, 15 E. 58th St., New York 22.

Further information regarding the Symposium can be obtained by writing to the above address.

HEMORRHAGIC INFARCTION OF TESTIS IN NEWBORN

Relationship to Testicular Torsion

CAPT. JIMMIE L. RHYNE (MC), U. S. Army Reserve
LIEUT. COL. FRANK A. MANTZ Jr. (MC), U. S. Army
and
COL. JOHN F. PATTON (MC), U. S. Army

THE FINDING of a tumefaction within the scrotum of a child is a distressing experience to parents and demands the utmost clinical diagnostic acuity of the attending physician. The urgency for prompt attention, usually through surgical approach, is stressed by all standard texts. The differential diagnosis includes congenital anomalies, vascular disturbances, traumatic injuries, infections, and neoplasms. An instance of firm testicular enlargement noted at birth in an infant delivered by Caesarean section and reflecting torsion of the spermatic cord serves as the basis of this brief report.

REPORT OF CASE

A white boy was delivered by Caesarean section after 37 weeks of gestation. The mother was an 18-year-old diabetic, who was adequately controlled on 85 units of isophane (NPH) insulin daily. The mother was a primagravida, blood Group A Rh-negative, serologic studies negative. The physical examination showed a large flabby infant weighing 3487 gm.; his skin and subcutaneous tissue appeared edematous and thickened, typical of infants born of diabetic mothers. Physical examination was otherwise normal except for examination of the genitalia, which revealed the presence of a stony, hard, firm, but smooth left testicular mass measuring 3.8 by 2.5 cm. (Fig. 1). The mass was adherent to the skin and could not be transilluminated. The spermatic cord appeared somewhat thickened; however, the mass did not extend along the spermatic cord. The right scrotum was normal, except for a small hydrocele.

Laboratory data showed the blood sugar level to range from 48 to 72 mg. per 100 cc. during the first two days of life; hemoglobin 15.1 gm.; RBC, 4,580,000; WBC, 10,800; differential count: polymorphonuclear cells, 55%; lymphocytes, 42%; monocytes 3%; hematocrit value, 42%. The infant's blood type was A Rh-positive; the Coombs' test was negative; 1 nucleated red cell per 100 white cells was seen. Serology was negative. Blood chemistry studies showed BUN, 11 mg. per 100 cc.; CO_2, 15.6 mEq.; chlorides, 114.5 mEq.; sodium, 148 mEq., and potassium, 6.1 mEq. X-rays of the chest, abdomen, and long bones were normal. Urinalysis was normal.

Fig. 1.—Newborn infant. Note enlargement and discoloration of left scrotum.

It was impossible for us to rule out the possibility of a testicular tumor; therefore, when the infant was 24 hours of age, the left scrotal region

From the Pediatric Service, Department of Medicine; Laboratory Service, and Urology Service, Department of Surgery, Fitzsimons Army Hospital, Denver.

was explored under local anesthesia, and the entire left testicle, epididymis, tunica vaginalis, and lower portion of the spermatic cord were found to have a dark blue necrotic appearance. These organs were removed along with 1.5 cm. of spermatic cord (Fig. 2).

The infant withstood the procedure well, and his postoperative course was uneventful with the exception of moderate jaundice, which was noted on the third postoperative day, and slight respiratory difficulty that responded to oxygen therapy and incubator care. On the third day of life the total serum bilirubin was 11.8 mg. per 100 cc. with 11.3 mg. as indirect-reacting bilirubin. He was placed

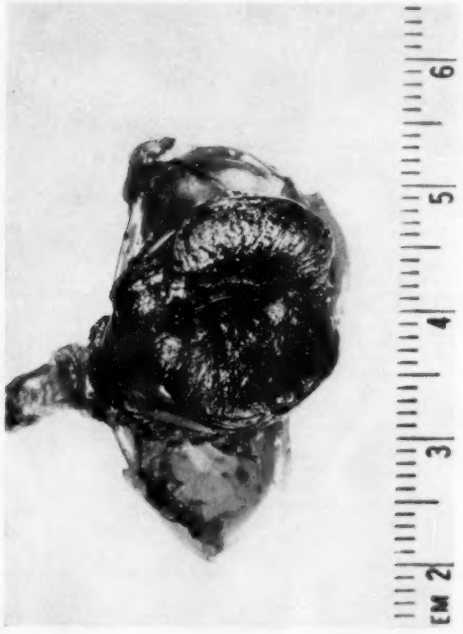


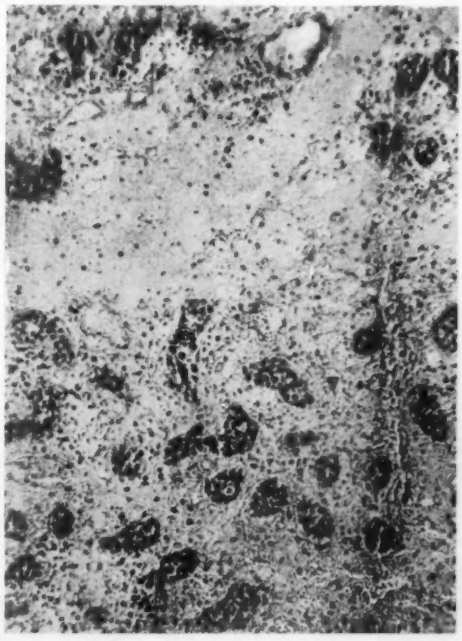
Fig. 2.—Gross appearance of testis. Note exudate on lining of tunica vaginalis and hemorrhagic necrosis of testicular parenchyma.

on penicillin and streptomycin prophylactically for three days postoperatively. The operative wound healed well, and the infant was discharged on the 12th postoperative day, with a weight of 3345 gm. He has been seen on several visits to the outpatient clinic and is following a normal course for a newborn.

Pathological Examination.—The specimen consisted of a totally excised infantile testis with tunica intact and included a 1.5 cm. segment of attached spermatic cord. The tunica vaginalis was thickened, edematous, turgid, and covered externally by numerous adhesions. Its contents included approximately 5 cc. of hemorrhagic fluid,

Fig. 3.—Spermatic cord. Note sharp line of demarcation and vascular dilatation in distal cord.

Fig. 4.—Testis. Hemorrhagic and necrotic changes in testicular parenchyma.



and abundant shaggy fibrinous exudate was noted on the lining. The testis and epididymis were enlarged, soft, and diffusely hemorrhagic and the tubules could not be lifted away. Extensive interstitial hemorrhage was noted at the junction of the cord and epididymis, above which the cord appeared unaltered and its covering tunic smooth. No distinct torsion or constriction was evident grossly.

Microscopic study confirmed a sharp line of demarcation in the distal portion of the cord below which extensive interstitial hemorrhage had occurred (Fig. 3). The testis and epididymis presented the histologic characteristics of diffuse hemorrhagic infarction with tubular necrosis and extensive extravasation of blood, much of which had hemolyzed (Fig. 4). In addition, there were many areas of calcification within the necrotic and organizing debris. No vascular occlusions were found. Rare focal areas of inflammatory infiltrate were scattered throughout the epididymis, consisting of lymphocytes, plasma cells, and polymorphonuclear cells. Scattered lymphocytes were noted throughout the testis. The tunica albuginea and vaginalis were edematous, fibroblastic, and hyperemic. The fibrinous exudate was undergoing early organization.

REVIEW OF LITERATURE*

A review of the English literature reveals only 12 reported cases of testicular infarction in the newborn period, the present case being the 13th. These cases are summarized in Tables 1 and 2.

* Statistical data include present case.

TABLE 1.—*Symptoms*

Reported Cases	Age	Weight, Gm.	Scrotal Mass and Overlying Skin	Pain or Tenderness	Testicle Affected	Other Abnormalities
Taylor, 1897	4 hr.	....	Mass 2 times size of opposite testicle; discolored at 24 hours; round & smooth; orchidectomy 2 days of age; P.O. uneventful	Slight	Right	Slight convulsions
Nash, 1921	5 days	....	Swelling of scrotum; skin blue, veins dilated; testicle adherent to skin; cord thickened to external ring, where nodule present; orchidectomy 11th day; P.O. uneventful	Present	Right	.....
Begg, 1921	2 days	....	Swollen testicle, hard & elastic, scrotum dusky violet, skin adherent, cord hard & knotted; orchidectomy 11th day; P.O. uneventful	.....	Right	.....
Golden & Hamilton, 1934	5 wk.	3693	Mass 5 by 2½ cm.; no transillumination, skin indurated & edematous; orchidectomy, herniorrhaphy, appendectomy; P.O. diarrhea 5 days	Present along with irritability & vomiting	Right	Inguinal hernia, appendicitis
Campbell, 1937	2 mo.	....	Enlarged testicle noted since birth, smooth & round; biopsy left	None	Bilateral	.....
Rosenblatt & Buerman, 1939						
Case 1.....	1 mo.	....	Mass right groin; orchidectomy & herniorrhaphy; P.O. uneventful	.....	Right	Strangulated inguinal hernia
Case 2.....	3 wk.	....	Strangulated inguinal hernia; orchidectomy & herniorrhaphy; P.O. death 50 days P.O., due to intestinal obstruction	Vomiting & bloody stools	Right	Strangulated inguinal hernia
MacLean, 1943						
Case 1.....	Birth	3575	Mass 3.5 by 2 cm., smooth & elastic, adherent to skin; no transillumination, skin ecchymotic; orchidectomy 14 days of age; P.O. scrotal abscess on 8th P.O. day	.....	Left	Mother had postpartum hemorrhage
Case 2.....	Birth	4423	Mass 3 by 2 cm., stony hard, no transillumination, not adherent, skin bluish green; orchidectomy 10 days; P.O. uneventful	.....	Right	.....
Ravich, 1947	Birth	3629	Mass 2.5 cm. diameter, firm, no transillumination; orchidectomy 15th day of life; P.O. uneventful	.....	Right	Left hydrocele
Campbell, 1948						
Case 1.....	3 days	....	Scrotum swollen, edematous, skin adherent, cord thickened; orchidectomy; P.O. uneventful	Present	Right	.....
Case 2.....	17 days	....	Mass 3 by 2.5 cm., hard, skin red & adherent; orchidectomy; P.O. uneventful	.....	Right	.....
Present case	Birth	3487	Mass 2.5 by 3.8 cm., stony hard, adherent to skin; no transillumination, skin reddish discoloration; orchidectomy 1 day of age; P.O. uneventful	None	Left	Right hydrocele; maternal diabetes

Among the 12 reported cases a mass was found at birth in only three instances. This is a report of the fourth case. The present case was the only one in which the testicle was removed by the second day of life. In spite of early operation, ischemic necrosis of the testicle was found. All the cases reported showed infarction or gangrene of the involved testicle, and no case of torsion during the newborn period was discovered in which the testicle was found viable. It should be emphasized that if any of these testicles are to be saved in the newborn period after torsion of the spermatic cord then early operation is mandatory. The average period from when the mass was detected until time of surgery in these reported cases was 13.6 days. As repeatedly noted, gangrene develops within 48 to 72 hours following torsion of the spermatic cord.

The infants' weight apparently plays no role in these reported cases. This entity has never been reported in a premature infant. The average weight of the five patients in which it was recorded was found to be 3761 gm.

A scrotal mass was present in all cases reported. The average size in the six cases in which it was recorded was 3.4 by 2.3 cm. The skin overlying the mass was discolored in 7 of the 13 cases. In no case was the mass irregular; however, a knot was noted along the cord in one case. The mass was stony hard, or firm, in 5 of the 13 cases and adherent to the skin in 5. In all of the cases in which transillumination was recorded none of the masses could be transilluminated. Pain or tenderness was detected when the mass was manipulated in 4 of the 13 cases. The usual picture is that of an asymptomatic scrotal mass. Associated symptoms in these patients were slight convulsions in one and irritability with vomiting in another.

TABLE 2.—*Clinical and Pathological Findings*

Cases Reported	Hgb., Gm./ 100 Cc.	WBC	Pathological Findings	Etiology
Taylor, 1897	....	.....	"Insertion of cord appeared like stalk of apple"; shiny fibrous constriction above testicle; testicle engorged; tunica & whole testicle full of coagulated blood; clot runs to ¼ in. of twisted cord above tunica vaginalis	Torsion of spermatic cord (extravaginal)
Nash, 1921	....	.....	Testicle purple; marked congestion of tunica vaginalis albuginea; extravasation of testicular substance on cross section	? Torsion of spermatic cord
Begg, 1921	....	.....	Gangrene of testicle with fluid in center	Double twist of spermatic cord
Golden & Hamilton, 1934	....	15,000	Testicle hemorrhagic & normal architecture destroyed; acute inflammation of appendix and testicle	? Torsion of spermatic cord
Campbell, 1937	....	.....	Hemorrhagic orchitis	Obstetrical trauma
Rosenblatt & Buerman, 1939				
Case 1.....	....	.....	Hemorrhage & gangrene of testicle	Encroachment & pressure on cord by strangulated hernias
Case 2.....	....	.....	Acute hemorrhagic infarction	
MacLean, 1943				
Case 1.....	17	15,500 PMN 27%	Hemorrhagic infarction of testicle & epididymis	Folded fibrous band at upper margin of epididymis
Case 2.....	18	9,850 PMN 40%	Hemorrhagic infarction of testicle & epididymis	Constriction at junction of spermatic cord in epididymis by all elements of cord
Ravich, 1947	14.4	18,000 PMN 65%	Hemorrhagic infarction of testicle & epididymis	Spontaneous, ? torsion of spermatic cord with spontaneous release
Campbell, 1948				
Case 1.....	19.5	15,850 PMN 89%	Hemorrhagic gangrene of testicle, epididymis, & tunica vaginalis	Torsion of spermatic cord 180 degrees (extravaginal)
Case 2.....	11.6	20,000 PMN 61%	Hemorrhagic gangrene of testicle, epididymis, & tunica vaginalis	Torsion of spermatic cord (extravaginal)
Present case	15.1	10,800 PMN 55%	Ischemic necrosis of testicle & epididymis	Spontaneous ? intrauterine torsion of spermatic cord

The right testicle was involved in 10 of the 13 cases, and in 1 case both testicles were affected. The patient demonstrating the bilateral involvement was reported by Campbell,[5] and the diagnosis was obstetrical trauma. In this patient a biopsy of the left testicle was obtained and showed hemorrhagic orchitis.

With the exception of this one case reported by Campbell, orchidectomy was performed in all cases. In only one was death reported postoperatively; that was a patient who had an associated strangulated inguinal hernia, and death was attributed to intestinal obstruction on the 50th postoperative day. One patient developed diarrhea postoperatively, and another, a scrotal abscess on the eighth postoperative day.

Three of the 13 cases reported had an associated inguinal hernia. In two of these cases [6] the hernias were strangulated and the authors were of the opinion that the infarction was caused by the encroachment and pressure of the strangulated hernia on the spermatic cord. In the other case associated with an inguinal hernia [4] it was the authors' opinion that the infarction was most probably caused by torsion of the spermatic cord. In the latter case the appendix was inflamed, and an appendectomy was performed.

A hydrocele involving the opposite testicle was noted by Ravich [8] and also occurred in the present case. The hydrocele was repaired surgically by Ravich, because he felt there was a strong possibility of torsion developing in the testicle with a hydrocele. We did not elect to repair the hydrocele in this case at the present time, because there was no obvious testicular compression and there is a good possibility in a newborn infant that the hydrocele will disappear spontaneously.

Our patient was born of a diabetic mother. It has been well established that infants of diabetic mothers have an increased incidence of congenital anomalies; however, this condition has never been described in such an infant, and we feel that most probably the maternal diabetes did not play a role in this case.

The hemogram when reported was essentially within normal range. Including the present case, there were two cases of relatively low hemoglobin levels recorded for the age of the infants [9]; however, there was no evidence of blood dyscrasia or thromboembolic phenomena determined in any of the 13 cases. The white cell count was markedly elevated in only one case,[9] and in this case a necrotic lower pole of the scrotum was noted after aspiration of the scrotal mass by an osteopath. It was also in this case that the low hemoglobin value was obtained.

Torsion of the spermatic cord was definitely demonstrated in four cases and strongly suspected in four others, including the present one.

COMMENT

The cause of the testicular infarction in this case and in most of those reported in the newborn is superficially obscure. When one considers, however, the sharp line of demarcation between hemorrhagic and nonhemorrhagic tissue in the spermatic cord, where no constrictive lesions or vascular occlusions were demonstrated either by the surgeon or the pathologist, the likelihood of torsion is inescapable. It is suspected strongly that careful study of ostensibly idiopathic testicular infarction in the newborn, when local maceration can be excluded, would yield similar conclusions in almost all cases.

The factors predisposing to testicular torsion in general are those of an unusually spacious scrotum; high investment of the tunica vaginalis on the spermatic cord; a long mesorchium; a long, lax, or absent gubernaculum; abnormalities of the epididymis, and anomalous attachment of the testicular mesentery or blood supply. With the probable exception of a spacious scrotum, no such defects existed in this case nor are they described in those of frank torsion heretofore reported in the literature. It appears significant that the tunica vaginalis was involved in the process of infarction, strongly suggesting that rotation was extravaginal. Campbell [9] has emphasized this point in conjunction with the observation that the tunica

vaginalis in infancy lies unattached in the scrotum, from which it can be separated without dissection. Such lack of attachment permits freedom of rotation limited only by the capacity of the scrotal pocket, which in most instances fortunately is minimal. It is considered likely that some intrauterine stimulus produced cremasteric contraction which resulted in rotation of the gonad and its investments. Although detorsion occurred, vascular interference had existed for a sufficient period to produce irreversible damage.

SUMMARY AND CONCLUSIONS

A case of hemorrhagic infarction of the testis, epididymis, and tunica vaginalis in a newborn infant is recorded, and the literature is reviewed.

The observation of a sharp line of demarcation in the distal spermatic cord and the involvement of the tunica vaginalis without local constriction or vascular disease suggest extravaginal torsion as the etiological factor.

The presence of the lesion at birth establishes it as intrauterine at onset.

Conditions predisposing to torsion in general and in the infant in particular are cited. It is suggested that torsion is a prominent cause of testicular infarction in the newborn when direct trauma during childbirth can be excluded.

REFERENCES

1. Taylor, M. R.: A Case of Testicle Strangulated at Birth, Brit. M. J. **1**:458, 1897.

2. Nash, W. G.: Torsion of the Testis in an Infant, Brit. M. J. **1**:267, 1921.

3. Begg, R. C.: Torsion of the Testis Occurring During or Immediately After Birth, Brit. M. J. **2**:843, 1921.

4. Golden, J. L., and Hamilton, H. H.: Strangulated Inguinal Hernia with Unusual Complications in Infant of 5 Weeks: Report of Case, New England J. Med. **210**:857, 1934.

5. Campbell, M. F.: Pediatric Urology, New York, The Macmillan Company, 1937, Vol. 2.

6. Rosenblatt, M. S., and Buerman, W. H.: Strangulated Hernia with Acute Hemorrhagic Infarction of Testicle in Infants, Northwest Med. **38**: 18, 1939.

7. MacLean, J. T.: Hemorrhagic Infarct of the Testicle in the Newborn, Surg., Gynec. & Obst. **76**:319, 1943.

8. Ravich, R. A.: Hemorrhagic Infarction of the Testicle in the Newborn, J. Urol. **57**:875, 1947.

9. Campbell, M. F.: Torsion of the Spermatic Cord in Newborn Infant, J. Pediat. **33**:323, 1948.

10. Campbell, M. F.: Clinical Pediatric Urology, Philadelphia and London, W. B. Saunders Company, 1951.

11. Nelson, W. E.: Mitchell-Nelson Textbook of Pediatrics, Ed. 5, Philadelphia and London, W. B. Saunders Company, 1950.

Progress in Pediatrics

PRESENTATION OF THE JOHN HOWLAND MEDAL AND AWARD OF THE AMERICAN PEDIATRIC SOCIETY TO DR. BELA SCHICK

At the Sixty-Fourth Annual Meeting, May 3, 1954, Buck Hill Falls, Pa.

INTRODUCTION AND PRESENTATION BY DR. HORACE L. HODES

IT GIVES me the greatest pleasure to announce that the American Pediatric Society has selected Dr. Bela Schick to receive the John Howland medal and award.

The Society offers this tribute to one of the greatest of pediatricians. The accomplishments of Bela Schick need no enumeration for this audience; no portion of the field of pediatrics has not been lighted by his genius. I shall, therefore, only touch upon a few phases of the career of this great scientist and pediatrician.

Bela Schick received his medical degree from Karl Franz University, at Graz, in 1900, when he was 23 years old. After a period of six months in the Austro-Hungarian Army, he returned to Graz, where he became a voluntary assistant in the clinic of Professor Escherich. From the first, he was considered a very exceptional physician by all his associates. Professor Escherich valued him most highly, and Schick was invited to accompany the great professor to Vienna when Escherich accepted the chair of Pediatrics there, in 1902.

In Vienna, Schick was appointed volunteer, or intern, to Clemens von Pirquet, who was resident physician at the Children's Clinic of the University. At once a firm friendship sprang up between the two men, which lasted until von Pirquet's death, in 1929. In 1902, they began the study of serum disease together. They explained serum sickness on the basis of an antigen-antibody reaction, an idea which they themselves realized was revolutionary. They stated:

> The conception that the antibodies, which should protect against disease, are also responsible for the disease, sounds at first absurd. This has as its basis the fact that we are accustomed to see in disease only the harm done to the organism and to see in the antibodies solely antitoxic substances. One forgets too easily that the disease represents only a stage in the development of immunity, and that the organism often attains the advantage of immunity only by means of disease.

Their observations on the immediate and accelerated reactions which occur on reinjection of serum were of profound importance and led directly to their basic concepts of immunity, hypersensitivity, and allergy. Their ideas regarding the relationship of the accelerated reaction to immunity are summed up in their book "Serumkrankheit," in the following paragraphs:

> We possess, therefore in the immediate or accelerated reactivity, a new criterion for the diagnosis that a patient has formerly had the same disease. This statement is not only valid for serum sickness, but, as we shall see for many other toxic and infectious diseases such as tuberculosis. We refer in this respect particularly to the behavior of the human to revaccination.
>
> The accelerated reactivity is the permanent advantage the organism has acquired by having overcome the first disease. Immediately after the termination of the disease the organism is in the stage of free antibodies in consequence of which we observe the immediate reactivity and hypersensitiveness. This phase has only a limited duration. The free antibodies disappear, but

in spite of it the individual is immune. But the essence of this immunity does not lie anymore in the immediate reaction against the infectious germ, but in an accelerated reproduction of antibodies.

This ability to localize a repeated infection does not rest on the presence of free antibodies in the body fluid but upon a property of the cells acquired through the first disease.

It is noteworthy that Schick was 28 and von Pirquet 31 years old when these conclusions were published. From Dr. Edwards Park, who knew both men, I have tried to learn something of the intellectual relationship which existed between them. Dr. Park has written as follows:

I doubt if they could answer this question themselves, but I have always suspected that their minds in some remarkable way complemented each other. Although it is impossible to analyze the "marriage of true minds" which existed between them, the importance of their combined contributions to medical science is clear enough. In my opinion at least their studies of immunity represent the finest contributions to medicine ever made by pediatricians. They perceived and defined the general principles of immunity as developed in their investigations of serum sickness, then of vaccination against smallpox, and finally tuberculosis. I do happen to

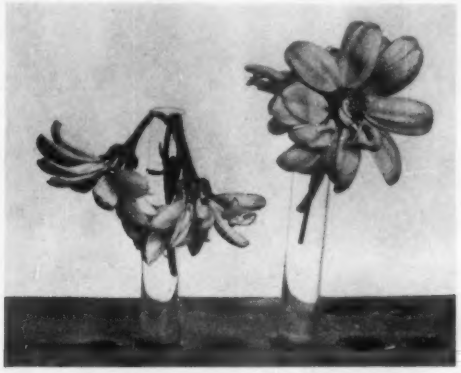


Fig. 1.—Photograph taken from a paper by Macht in the *Journal of Pharmacology and Experimental Therapeutics* **22**:413, 1924. In this paper, Macht described his confirmation of Schick's findings on menotoxins and referred to Schick's work on this subject, which was first published in 1920.

know that Schick was the one to perceive the nature of the accelerated reaction, a concept difficult to grasp, and of obvious basic importance. I doubt if knowledge in this field has advanced much further, except in details, than when Schick and von Pirquet left it.

My own impression, gained from conversations with Dr. Schick, is similar to Dr. Park's. The researches of Schick and von Pirquet were so interwoven that, with a little different arrangement of circumstances, we might have had the Schick tuberculin test and the von Pirquet test for immunity to diphtheria.

I shall not attempt here to evaluate Bela Schick's contribution to the conquest of diphtheria. The discovery of the Schick test was no accident; it stemmed directly from careful planned observations and experiment. It should be noted too that Schick knew at once that the reaction could not be of the same nature as the reaction to tuberculin.

I am certain that the simplicity and the practical value of the Schick test delighted the heart of its discoverer. Dr. Schick enjoys useful scientific discoveries, and his friend Rene Dubos has applied to him the following quotation from Pasteur: "To him who devotes his life to science, nothing can give more happiness than making

discoveries, but his cup of joy is full only when the result of his studies finds practical application." [1]

However, we must not conclude from his devotion to things practical that Bela Schick believes that research must always have a specific end in view. In fact, he has several times warned of the danger of such a course. He has told me that his great chief Escherich overlooked an important finding on one occasion because of pursuit of a limited goal. Dr. Schick says that the discoverer of Escherichia coli became so engrossed in his study of this organism that he discarded all bacteria which did not produce gas in lactose. In this way he threw away the dysentery bacillus—to the great advantage of Flexner.

Dr. Schick's keen interest in all natural phenomena led to his demonstration of menstrual toxins (Fig. 1). One day a grateful patient sent him a bouquet of

Fig. 2.—Dr. Bela Schick. Portrait by Leo Katz.

fresh red roses. Dr. Schick asked a woman attendant to place the flowers in a vase of water. At first she refused to comply with the request, but on Dr. Schick's firm insistence, she finally did so. In a few hours the firm, fresh roses were wilted and dead. Dr. Schick could not permit so interesting a happening to pass without investigation, and on inquiry, he learned that the attendant was menstruating. She stated that her reluctance to handle the roses was due to her knowledge that flowers always died when she touched them during her periods. On going into the subject, Schick found many popular beliefs based on the idea that women exuded poisons during menstruation. For example, it is believed that bread dough kneaded by menstruating women fails to rise and that fruit preserved by them always spoils. During menstruation women are not permitted to work in perfume factories; they are not permitted to handle silk worms or to pick mushrooms. Schick found similar ideas expressed in the Bible and in the writings of Shakespeare, Pliny, and other authors. He found summaries of the folklore on the subject in "Das Weib," by Plosis-Bartels, and in Frazer's "Golden Bough." The idea that menstruating women

were poisonous to living things was generally regarded by educated people as a superstition. No one, in modern times at least, ever made a scientific study of the subject until Bela Schick did so. He showed that the skin of menstruating women did in fact excrete substances which hasten the death of flowers, and he showed that this effect may be prevented by wearing of sterile gloves. He demonstrated that these toxins circulated in the blood. Of particular interest was his finding that the addition of a small amount of blood from a menstruating woman prevented the growth of a culture of yeast cells, while blood obtained at other times had no such effect. Dr. Schick published his observations on menotoxin in 1920. His paper contains the characteristically modest statement that the priority of the discovery of menotoxin belongs not to him but to folklore.

Dr. Schick came to New York in 1923 to become chief of pediatrics at the Mount Siani Hospital. He was welcomed with great enthusiasm by his new staff. Close ties of friendship were established at once, and a happy friendly atmosphere rapidly came into being. The effect of his teaching and stimulation upon his colleagues and pupils was most profound. On many occasions, Dr. Bass, Dr. Kohn, and Dr. Karelitz, of this Society, have described the strong effect upon their thinking which Dr. Schick exerted. Dr. Schick retired from his post as chief of pediatrics at Mount Sinai in 1942, but we still regard him as an active member of the department. In 1950 he became pediatrician-in-chief at Beth El Hospital—a position he still holds.

I have not attempted a minute analysis of Bela Schick's genius, nor shall I try to define in detail his wonderful personal qualities. His modesty and friendliness, his joy and humor, make friendship with him a pleasurable experience of the rarest quality. Of him we may use the opening words of Christopher Smart's "Song to David": "Sublime invention, ever young—of vast conception— Unrivall'd royalty of thought, O'er meaner strains supreme."

Bela Schick, great scientist and pediatrician, beloved friend and teacher, I present to you on behalf of this society the John Howland medal and award.

ACCEPTANCE BY DR. BELA SCHICK

I AM AWARE of the fact that the John Howland Medal and Award is one of the highest distinctions which a Pediatrician can achieve, and I am therefore deeply impressed that the council of the American Pediatric Society has found me worthy of such a great honor.

John Howland died on June 20, 1926. In the obituary, Dr. Abt and Dr. Park said that pediatrics had lost a leader who was one of the ablest and most distinguished of his generation. He was the first pediatrician who, besides being a well-grounded clinician, was a pathologist, chemist, and investigator. He was a teacher of teachers, influencing greatly American pediatrics. A group of his pupils, excellently trained by him, are carrying on his high standard. I know how difficult it was at that time to bring pediatrics up to the same level as internal medicine. For many years pediatricians had to fight to have pediatrics recognized as an independent specialty separated from internal medicine. In the old world, pediatricians were engaged in the same fight. Howland's work on rickets shed new light on this problem. His knowledge of chemistry enabled him to recognize and understand acidosis, an entirely new field of body chemistry. The American Pediatric Society lost a great leader by his untimely death. Howland was only 53 years when he died.

To honor the memory of such a great man and do him justice is difficult. In my talk to you, I intend to discuss three pediatric problems which are near to my

heart. Two of them are relatively easy to study; the third problem will be taken up later. Since my Viennese days, when I had the opportunity to study newborn children, I have been interested in the problem of prolonged gestation and therefore in the problem of overmature newborn babies. Whereas Clifford studied with extreme care and exactness the disadvantages and dangerous aspects of the problem, I am interested in the beneficial effect of prolonged gestation. There is no doubt that the whole problem involves the function of the placenta as to whether it is adequate or insufficient. As long as the placenta is in full function and able to take care of the requirement of the fetus, not only is no harm done, but possibly some good. The termination of pregnancy is a mysterious affair. I have always had the impression that it would be of no disadvantage for the fetus to remain a little longer in the uterus. The human newborn is not capable of caring for himself but is still in "extrauterine dependence" upon the mother or some other kind person. Everybody who reads Clifford's classic description of the miserable creatures born overmaturely realizes that this form of overmaturity is most undesirable. The children are poorly nourished, are rather thin and long, and have a dry parchment-like skin which is desquamating; there is no vernix caseosa, and the skin is dark yellow. All these symptoms are due to the fact that at approximately the 40th week of pregnancy the function of the placenta deteriorates rapidly. The nutrition and, therefore, the development of the child are endangered. The fetus has to keep itself alive by using its own reserve of fat. An overmature child may therefore be reduced in weight. The mortality of such children is high.

As I mentioned before, I am interested in the beneficial aspect of prolonged pregnancy. These children have experienced a normal function of the placenta. The child's situation is therefore very favorable. It has been a kind of paradise, or Shangri-La. Such an overmature newborn baby looks very good; the skin may be a little dry at certain places and the vernix caseosa reduced in amount, but the skin is white, like the skin of an older infant, and the turgor of the skin and of the subcutaneous tissue is very good. The organism is better supplied with all the necessary substances, such as subcutaneous fat and minerals which are normally deposited during the last weeks of pregnancy in rather insufficient amounts; overmature children have no or almost no icterus neonatorum. The baby is alert, usually has its eyes open, looks bright, and seems to be more interested in its surroundings. It takes nourishment much better than the average newborn baby. Most of the children are overweight; a weight of over 9 lb. (4,080 gm.) is frequent. The outstanding objective sign of longer gestation is better development in length. The infant might measure 52 to 57 cm. and more.

I realize how difficult and how unreliable the calculation often is to determine the duration of pregnancy. There is much literature concerning overmature children. But the interest is rather concentrated on the legal aspect relating to the problem of paternity.

My attention to the problem was aroused by my study of newborn children delivered by Caesarean section. Indication for this kind of delivery was very strict and was frequently due to a disproportion of the pelvis to the size of the head of the child. Since in such cases no special hurry exists to terminate the pregnancy, the operation was often postponed. The child remained longer within the uterus. Such children had the appearance that I described before.

It has been my experience that beneficial effects due to overmaturity are much more frequently encountered (about 16% of our newborn infants) than the damag-

ing ones so excellently described by Clifford. He points out that primiparae and older women are more prone to give birth to a child with deleterious effect of prolonged gestation.

I pointed out that the group of better developed overmature children do not as a rule show icterus, or if so very slightly. I should like to explain this fact in the following way. Icterus neonatorum is, as I have pointed out, a by-product of the synthesis of the hemoglobin of the fetus. At the time of premature termination of the pregnancy, there is still present a great amount of hemoglobin derivates, including bilirubin, which passes the placenta. This is the reason why premature babies develop more intensive icterus neonatorum and are anemic. As the pregnancy progresses, the delivery of hemoglobin derivates comes to an end. When the child is overdue, he has completed the synthesis of his own hemoglobin. The splitting off of bilirubin no longer occurs, and no icterus develops. Lately, a child was born in Atlanta, Ga. with a birth weight of 14 lb. 7 oz. (6,550 gm.). The length of the child was 57.5 cm. It was the third child of a healthy mother. She was not a diabetic, nor was there any diabetes in the family history. Part of the enormous weight was due to edema, and during the first few days the child lost about 2 lb. (910 gm.) of edema. The delivery was carried out without instruments. There were no complications. The child looks well and is alert and apparently strong. According to the mother, the birth occurred six days late. But most probably the calculation was incorrect. The length of the last overmature newborn infant observed by me was 61.5 cm. The weight was 13 lb. 14 oz. (6,300 gm.).

The second problem I wish to discuss is the use of pooled gamma globulin in infectious diseases in childhood refractory to antibiotics. I have studied this problem for more than two years with Dr. Harris.

In 1952, Bruton reported the observation of an 8-year-old child who suffered numerous viral and severe bacterial infections and showed evidence of deficient antibody production. No gamma globulin was found on electrophoretic studies, in spite of relatively normal levels of total serum protein. After this report, a small number of cases with similar histories were seen by other authors (Janeway and his collaborators). With the exception of a normal response to vaccination with smallpox vaccine, there was no response to artificial immunization with a variety of agents. These reports of cases of agammaglobulinemia were followed by observations of other authors who found patients with transient or partial deficiency of gamma globulin.

The discovery and use of antibiotics has brought about a revolution in the treatment of bacterial diseases. On the other hand, their effect against viral diseases, though not entirely negative, is still not satisfactory. In cases of agammaglobulinemia, periodic injections of gamma globulin obtained from pooled sera produced a striking protection against a variety of infections.

In contrast to the rare instances of permanent agammaglobulinemia, the practitioner encounters a number of cases where the infectious process does not respond satisfactorily to treatment with sulfonamides or antibiotics. Globulin studies do not indicate that the patient is suffering from any form of deficiency of gamma globulin.

Even changing the antibiotics may not improve the condition. The treatment seems to have reached a dead end. The hypothesis is justified that these patients may have even a normal amount of gamma globulin, but the gamma globulin is deficient in the specific antibody needed against the particular infection. Because of the

large variety of antibodies carried by pooled gamma globulin, the injection of this material offers a method of treatment of prolonged bacterial and viral infections which do not respond to sulfonamides or antibiotics. In our clinical study we found that the treatment of over 30 cases with pooled gamma globulin was effective in the majority of patients. Six tenths to 0.8 cc. per kilogram of body weight was a satisfactory dose.

I now come to the third problem which I should like to discuss. It is the problem of prevention of premature termination of pregnancy. I hesitate to talk about my ideas because they are up to the present almost entirely theoretical. Experiments to support the theory are not conclusive. The first question which arises is; What starts the birth of a baby? There is not much written about it. In the handbook of Davis on "Gynecology and Obstetrics" I found the following remarks: "Just why a given woman goes into labor at a particular time is not known. It would seem that the growing distention of the uterus might be a factor. Likewise an increased irritability of the uterus musculature initiated in early pregnancy might be another factor." It can not be claimed that this explanation is very satisfactory.

I was very much interested in a paper read by Ludwig Hirszfield, at the International Pediatric Congress of 1950, in Zurich, dealing with serological conflicts between mother and child (fetus) in the light of immunology and genetics. These conflicts are, according to Hirszfield, responsible for the occurrence of habitual abortion in women. This paper as you see discusses the same problem: What is the cause of the onset of the contraction leading to the birth of the child?

The conclusions of Hirszfield are as follows. A survey of 491 families with habitual abortions and 54 families with cases of erythroblastosis showed that the incidence was not dependent on the compatibility or incompatibility of the OBA blood group of the parents. RH incompatibility between husband and wife, however, causes a rise in the incidence of abortions. The author showed that heterozygous mothers do not produce RH antibodies and cannot, therefore, give birth to infants with erythroblastosis. On the other hand, the possibility must be considered that sessile antibodies may cause an allergic sensitization. The total of possible incompatibilities is equal to the number of heterozygous subjects. Hirszfield treated patients suffering from habitual abortions with antiallergic drugs. His choice was antazoline (Antistine). He was able to prevent abortions in 75% of the cases.

I wish to refer to a classic experiment in allergy, the Schultz-Dale test. A virgin uterus can be sensitized with a foreign protein, for instance, with Orchard grass seed digest. The horn of the uterus responds with maximal contraction if the sensitizing foreign protein is added to the suspension fluid. It is known that each embryo or fetus has its own individual protein which is different from the protein of the mother. Thus every mother would be exposed to sensitization by the individual protein of her fetus. It is not necessary to assume the existence of circulating antibodies against this protein in the mother, but sessile antibodies in the uterus may be expected. The development of sensitization is a slow process, and so the degree of sensitization increases with the progress of pregnancy. A similar increase of sensitization is found in erythroblastosis.

Placental protein may act also as a foreign protein. It is interesting that in many animals epinephrine produces uterus contractions whether the animal is pregnant or not. But in the cat, rat, mouse, and guinea pig, as well as in human beings, the pregnant organ alone is contracted by epinephrine, the nonpregnant organ does not respond.

Some theories concerning the onset of uterus contractions have been published. Most frequently endocrine substances, particularly estrogen, progesterone, and thyroid, have been considered in combination with the aging and separation of the placenta (Reynolds). The insufficient function is believed to give the stimulating signal for the onset of the contraction of the uterus, terminating the pregnancy. Abnormalities of the uterus must be corrected.

I was interested to read that the approach to this problem on an allergic basis is not quite new. Urbach, in his excellent book on allergy, mentions that allergy was considered by some authors. Whereas Urbach has an incredible and very reliable list of over 2,000 references about other phases of allergy, he does not quote the name of any author writing on this subject. He refuses the very idea that allergy may be instrumental in starting the delivery of a baby.

There are some facts which have bearing upon my theory. In an article, Bram Rose mentions that although histamine is present in the tissues of animals and in human beings, it can only be demonstrated in the placenta of pregnant women. These observations of the presence of histamine in pregnancy are certainly interesting, although the role of histamine in allergy is still not entirely understood, particularly in relation to allergic reactions others than urticaria-like eruptions.

I wish to call attention to the fact that the course of allergic diseases is often profoundly influenced by pregnancy. The effect is extremely varied. Some patients are completely relieved of allergic manifestations, some are improved, others are unchanged or become definitely worse. Evidence that cortisone or a related substance may be formed by the placenta suggests an explanation for the effect of pregnancy upon allergic conditions. Sheldon, Lovell, and Matthews point to the possibility that injections for hyposensitization may produce uterine bleeding and even abortion. They agree with Hirszfield without quoting him that allergy may be a contributing factor in women who are subject to repeated spontaneous abortions. Histamine produces powerful contractions of the uterus muscle. It is also of interest that abortion can be produced by an injection of an antiplacental serum. Such a serum can be obtained by injecting placental tissue from one species of animal into another. Some instances of abortion and toxemia might be due to the development of antibodies against the placenta protein by the mother. This mechanism has not been demonstrated to occur in human beings.

I repeat the statement that there is a gradual increase in the histamine content of the serum during pregnancy, and a significant amount of histamine appears in the plasma at the time of delivery. This may be due to allergic antigen-antibody reaction.

We see how difficult it is to explain the cause of the normal termination of pregnancy. It is still more difficult to explain the cause of premature termination. All our procedures are concerned with the salvation of a prematurely born baby. The solution of the problem of prematurity is to prevent the premature termination of the pregnancy. The method to be used in our attempt would seem to be the use of antiallergic procedures. Whether or not antazoline is the most suitable remedy will have to be investigated. Other procedures should be considered. The present methods of prevention—bed rest, application of endocrine substances, etc.—should be continued.

It will be my duty to study experimentally whether we can again establish the existence of a specific protein in the newborn. The most important experiment will be to demonstrate whether or not the Schultz-Dale phenomenon exists in the human uterus. Muscle strips of the human uterus obtained from a Caesarean section will be used, exposing the strips to the navel cord serum of the newborn.

I am now at the end of my discussion of pediatric problems. Discussing the problem of preventing prematurity is in line with our usual pediatric thinking of prevention. I am aware of the difficulty of proving my theory. I expect even that the allergic approach might not be the exclusive way. Allergy may be only the initial spark to initiate the chain reaction of contractions of the uterus. The importance of the existence of different individual proteins of mother and child for creating allergic interaction between antigen and antibody must be underlined.

In case my theory could bring about a progress in the problem of preventing prematurity, I should feel that I had paid the right tribute to the memory of Howland. Again, I wish to thank you most sincerely for having bestowed upon me the John Howland medal and award.

REFERENCE

1. Gronowicz, A.: Bela Schick and the World of Children, New York, Abelard-Schuman, Inc., 1954.

News and Comment

ANNOUNCEMENTS

Nassau Pediatric Society.—There will be a scientific meeting of the Nassau Pediatric Society on Monday, Feb. 14, 1955, at 9 p. m., at Felice's Restaurant, Westbury, L. I., N. Y. The guest speakers will be Earle G. Brown, M.D., Public Health Facilities; Herbert S. Whiting, M.D., Rehabilitation; Alan A. Jaques, M.D., Facilities for Retarded Children. They will talk on allied services available to the Pediatrician in Nassau County.

The University of Texas M. D. Anderson Hospital and Tumor Institute, Program of Cancer Fellowships and Residencies.—Facilities and equipment for therapy and research in the field of malignant diseases are provided for qualified applicants seeking training and research opportunities in oncology: 80,000 feet of space devoted to research, clinics equipped to handle 100 new patients and 200 revisits daily, a Cobalt-60 Irradiator and Betatron, and radioactive isotope facilities. Fellowships and residencies are under the auspices of The University of Texas Postgraduate School of Medicine. Participation in fundamental cancer research under able guidance, as well as a broad program of education in the Texas Medical Center, is offered in the following divisions:

Diagnostic radiology
Therapeutic radiology
Anatomical pathology
Clinical pathology
Experimental pathology
Medicine
Experimental medicine
Surgery
Experimental surgery
Malignant diseases (rotating)
Anesthesiology
Biochemistry
Pediatrics
Gynecology
Physics
Neurological surgery

For further information and application forms write to Grant Taylor, M.D., Office of Education, The University of Texas M. D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston 25, Texas.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

PROTEIN, CALCIUM, PHOSPHORUS, AND MAGNESIUM CONTENT OF NURSERY SCHOOL LUNCHES, INCLUDING "SECONDS." MAEONA LEE COX, BETTY DANIELS SPENCE, and FLORENCE I. SCOULAR, Child Developm. **24**:181 (Sept.-Dec.) 1953.

The nursery school lunches analyzed, includings "seconds," for a best and poorest eater in each age group provided an average of 11.57 and 8.07 gm., respectively, of protein for the younger group and 10.13 and 10.48 gm., respectively, for the older group.

The foods supplied to all of the children about 0.5 gm. of calcium but only 0.33 gm. of phosphorus.

The magnesium supplied ranged from 98 to 122 mg. It is assumed that this amount represents about one-half of the daily requirement of this age group.

FROM THE AUTHORS' SUMMARY.

SEX DIFFERENCES IN BASAL METABOLIC RATE. STANLEY MARION GARN and LELAND C. CLARK JR., Child Developm. **24**:215 (Sept.-Dec.) 1953.

In order to determine whether the sex differences in the basal metabolic rate could be explained in terms of body size and body composition, 409 determinations of basal oxygen consumption were made on 76 boys and 69 girls, including 27 pairs matched on the basis of muscle size.

In the age span of 6 to 17 years, the boys increased in basal oxygen consumption from 1,145 Cal. per 24 hours to 1,841, an increase of 60%. The girls showed an increase of only 30% in the same period.

Correcting for body size through the use of a uniform reference standard (Calories per kilogram), the magnitude of the sex differences was reduced. However, the boys still exhibited a higher metabolic activity, especially in the older groups, with differences up to 10%.

Although matching on the basis of muscle mass was satisfactorily corrected for sex differences in body composition (namely muscle mass), the discrepancy in oxygen consumption remained, especially in the older group. With a mean difference of only 0.05 mm. in muscle size, the mean difference in oxygen consumption for the pairs (74.4 Cal. per 24 hours) equaled 6%.

It was concluded that the higher level of metabolic activity in the male is not entirely due to his greater body size or to his higher proportion of muscle per unit of mass.

Attention was directed to the metabolism-stimulating effect of certain steroid hormones, which may underlie the residual sex differences in basal metabolism, and to the epidemiological implications of the higher level of metabolic activity in the male.

FROM THE AUTHORS' SUMMARY.

ORAL TEMPERATURE AND SUBCUTANEOUS FAT DURING ADOLESCENCE. DOROTHY H. EICHORN and JOHN P. MCKEE, Child Developm. **24**:235 (Sept.-Dec.) 1953.

Age trends and sex differences in oral temperature and subcutaneous fat among 53 boys and 52 girls measured from approximately age 11 years to age 18 years were examined.

Oral temperatures declined during this age period in both sexes, the decline being more marked, and approximately linear, in boys. Among girls the decline was reversed between the ages of 13 and 15½ years. After age 13 years, the girls' oral temperatures were significantly higher than those of the boys. No relationship between oral temperature and subcutaneous fat was observed in boys, though indications of a positive relationship were obtained in girls. Little relationship between oral temperature and the B. M. R. was observed in girls, though indications of a positive relationship were obtained in boys. When oral temperature was considered in relation to the menarche, it was found that the early decline in temperature reversed itself at the menarche, rising for about two years thereafter before resuming the decline. Subcutaneous fat in girls increased until the age of 16 years. Among boys, subcutaneous fat showed comparatively little systematic variation with age. The trend was curvilinear, increasing to age 12 years, declining somewhat from age 13 to about age 17, and then increasing again to age 18 years.

FROM THE AUTHORS' SUMMARY.

Vitamins; Avitaminoses

VITAMIN T (GOETSCH): A CLINICAL AND BIOCHEMICAL STUDY. S. NORDIO, Lattante **25**:342 (June) 1954.

Nitrogen balance studies with children and with rats indicate that the vitamin T (Goetsch) will stimulate the synthesis of protein, even when there is no gain in body weight.

HIGGINS, Boston.

ACUTE FORM OF HYPERVITAMINOSIS A. N. NAVARRO GARCIA and A. VALLS SANCHEZ DE PUERTA, Acta pediát. españ. **11**:667-688 (Aug.) 1953.

The authors present the detailed clinical history of seven infants suffering from an acute hypervitaminosis A. They describe the metabolism in the body of vitamin A.

The conclusions reached are as follows: 1. Symptoms of acute hydrocephalus may follow excessive dosages of vitamin A. 2. There is rarely a case of vitamin A deficiency in children under three months who are breastfed. 3. Deficits of vitamin A may exist in malnourished infants, in those who have suffered from acute nutritional illness, and in children who have repeated infections, especially upper respiratory infections. 4. Large doses of vitamin A are contraindicated in children under 3 months of age who are healthy, as well as in infants under 6 months who have had fruit and vegetables added to their diet.

Vitamin A should not be given to any children during acute febrile conditions and should not be resumed following these conditions until the temperature has returned to normal.

If it can be demonstrated that vitamin A deficiency existed before the acute infection, the vitamin A may be started as soon as the fever is gone. Thirty milligrams is enough for a well child. Large doses (60 mg.) should be used only in severe nutritional deficiencies secondary to intestinal disorders.

The authors report that one of their cases had been receiving nose drops containing vitamins A and D.

ALLEN, Santa Fe, N. Mex.

XEROPHTHALMIA IN SICK INFANTS DUE TO DEFICIENT ABSORPTION OF VITAMIN A. M. ZEVI, Nord. med. **49**:575 (April 17) 1953.

Report of three cases of xerosis conjunctivae and keratomalacia. The first infant had had gastroenteritis for a long period, the second had suffered from severe jaundice due to congenital atresia of the bile ducts, the third was a premature poorly developed infant who had jaundice for some weeks. It is maintained that the cause of the xerophthalmia must have been deficient absorption of vitamin A. In disease of this kind in infants, parenteral treatment with vitamin A should be given more often.

WALLGREN, Stockholm.

Prematurity and Congenital Deformities

CONGENITAL MALFORMATIONS: ETIOLOGY OF THE NONHEREDITARY FORMS. ALFRED SUNDAL, Nord. med. **50**:991 (July 16) 1953.

A survey is given of the nonhereditary congenital malformations, with special reference to findings obtained by animal experiments and to known etiological factors in human beings. The animal experiments have given a new and interesting insight into the etiology of congenital malformations, although such experiments cannot directly be applied to conditions which may lead to malformations. The author stresses that further investigations and the collection of clinical material on nonhereditary malformations are essential. Too little is known about factors such as chemical contraceptives, artificial insemination, intoxication with abortifacient drugs etc., all of which may have teratogenic effect (Author's summary).

WALLGREN, Stockholm.

SEASONAL VARIATIONS IN THE INCIDENCE OF PREMATURE DELIVERIES. GEORG KATZ, Nord. med. **50**:1637 (Nov. 26) 1953.

A comparison of the birth months of 228 premature babies with that of 4,516 full-term infants resulted in similar curves for the two groups. The curve for the prematures, however, lay about two months ahead of that for the full-term infants. This is consistent with the fact that the prematures in this series were born, on an average, one and one-half months before term.

WALLGREN, Stockholm.

INFANTILISM WITH AGENESIA OVARIAE AND OTHER MALFORMATIONS (TURNER'S SYNDROME). HILDA BLIX, Svenska läk.-tidning. **50**:64 (Jan. 9) 1953.

The author gives a description of three girls 15 years of age, with infantilism, increased excretion of gonadotropic hormone, decreased excretion of estrogen hormone, and a decrease or normal excretion of 17-ketosteroids. None of the children had pterygium colli. Treatment with diethylstilbesterol (Stilbesterol) produced improvement of the body length.

WALLGREN, Stockholm.

Newborn

NATAL DAY DEATHS. H. N. BUNDESEN, J. A. M. A. **153**:466 (Oct. 3) 1953.

In a study based on data on 10,000 neonatal deaths, Bundesen points out that to reduce needless infant deaths, most effort must be concentrated on the first three days of life and on infants of low weight, who die mainly from abnormal pulmonary ventilation and injuries at birth.

According to this study, there are seven major anatomic causes of death in the neonatal period: (1) abnormal pulmonary ventilation, (2) injuries at birth, (3) malformations, (4) infections, (5) blood dyscrasias, (6) anoxia, and (7) miscellaneous causes. Abnormal pulmonary ventilation and birth injuries were responsible for 83.5% of all the deaths on the first day in infants of low weight (under 1,500 gm.) in this series.

As a result of this analysis of the causes of death and the factors contributing to them in these infants, it is pointed out that concentration of effort is required, with complete cooperation of the patient, in improving prenatal care of women of low socioeconomic status, in constantly providing for skillful natal care of the mother in the hospital by obstetricians, and in providing for optimal postnatal care of the infant by pediatricians.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

STUDY OF INTELLIGENCE IN CASES OF RHESUS INCOMPATIBILITY. E. M. CREAK and MARJORIE DURWARD, Great Ormond St. J. (No. 6) p. 81, Dec., 1953.

Fifty patients were chosen at random from a group of 77 children who had had symptoms of Rh incompatibility at birth. Intelligence tests were given to determine whether the incompatibility was a cause of undifferentiated mental defect.

All of the children with mental defect or educational subnormality also had physical signs of brain damage.

MCGUIGAN, Evanston, Ill.

INCIDENCE OF APNEA AT BIRTH IN THE ENCEPHALOPATHIES OF CHILDREN. G. TARDIEU, M. R. KLEIN, J. P. HELD, and J. TRELAT, Rev. neurol. **89**:22, 1953.

Apnea at birth, occurring for at least 15 minutes, was used as the criterion for comparison of 629 children with cerebral defects with 280 control subjects. In the group with an I. Q. of less than 50, prolonged apnea was observed in 13.5%, but only 2.5% of the normal subjects had comparable apnea. Of 81 cases of infantile hemiplegia, 12% had apnea lasting more than 15 minutes, and 19% had apnea for less than 15 minutes. Among the patients with cerebral diplegia, 15% had apnea of more than 15 minutes.

BERLIN, Mount Vernon, N. Y. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

PROGNOSIS FOR REVIVED NEWBORN INFANTS. G. TARDIEU and J. TRELAT, Rev. neurol. **89**:259, 1953.

Of a group of 166 infants, 35 required resuscitation for less than 15 minutes. In this group 22.8% showed defects of mentation. Of the infants apneic for more than 15 minutes, five had motility disturbances, and of those apneic for less than 15 minutes, four had motility disturbances. Only 39.5% of infants who were apneic more than 15 minutes failed to have disorders of motility. The authors conclude that disorders of intelligence, motility, and behavior are more frequent and more serious in infants who are apneic at birth, especially if the apnea is longer than 15 minutes.

BERLIN, Mount Vernon, N. Y. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

PLASMA ELECTROLYTES IN THE NEONATAL PERIOD. T. STRENGERS, JOHANNA W. MAAS, H. ROTTINGHUIS, and G. A. FEHMERS, Acta pædiat. **43**:345 (July) 1954.

The plasma Na, K, Cl, and CO_2 levels were determined in 32 full-term and 30 premature infants, from the first to the seventh day, inclusive.

The full-term infants showed on the first day a slight acidosis, which disappeared gradually in a few days. The other values were the same as in adults.

The premature infants showed a normal Na and a slightly high K content, but they had a distinct hyperchloremic acidosis, which remained stationary during the first week.

The acidosis on the first day is ascribed to the residual effects of an anaerobic metabolism in utero or during birth. The hyperchloremic acidosis of the premature infants is ascribed to the physiological immaturity of the kidney with respect to the chloride clearance.

The electrolyte values in premature infants showed a large dispersion, which points to the lability of the premature infant in maintaining the equilibrium of plasma electrolytes.

FROM THE AUTHORS' SUMMARY.

Acute Contagious Diseases

IMMUNIZATION AGAINST DIPHTHERIA: THE BOOSTER DOSE. J. H. MASON, MARY ROBINSON, and MARGARET S. BROWN, South African M. J. **27**:293 (April 11) 1953.

The authors stress the need for booster doses to maintain adequate levels of antitoxin in previously immunized persons. They find that small intracutaneous doses are effective as boosters.

McGUIGAN, Evanston, Ill.

A SILENT EPIDEMIC OF POLIOMYELITIS. H. H. MALHERBE, South African M. J. **28**:68 (Jan. 23) 1954.

Following the occurrence of a case of fatal poliomyelitis, investigations were carried out on the children at the nursery school attended by the patient. There had been no known contact between the patient and any source of infection.

Stools were collected from 44 children in the school as well as two siblings who had come to the school daily at midday, and from three teachers and a student teacher.

The specimens from the teachers were all negative. Of the 46 children tested, 28 were positive for the Leon strain of poliomyelitis. Later studies showed 3% of the children to be excreting virus for at least seven weeks.

No cases of clinical poliomyelitis occurred in this group. McGUIGAN, Evanston, Ill.

MEASLES ENCEPHALITIS. JEAN CAMBIER, Presse méd. Supp. 2, p. 24 (Jan. 2) 1954.

Measles encephalitis does not, indeed, show those characteristics of "experimental disease" as does vaccinal encephalitis. In view of its frequency, diversity in its clinical aspects, and such problems of prognosis as it does raise, it deserves holding a prominent place in the field of posteruptive encephalitis. The author confines himself to the description of measles encephalitis properly so-called as clinically defined by the syndrome of scattered encephalomyelitis and as pathologicaly defined by those changes in leucoencephalitis with perivenous distribution. In order to point out the limitation of this affection the author discusses the nervous manifestations which may be interpreted in different manner according to their being connected either to "hemodynamic disorders," or to a malignant syndrome, or cerebral phlebitis, or metastatic suppurations.

Etiology, clinical and pathological features, pathogenesis, and prognosis are described and discussed. In a final section the question of treatment is studied.

FROM THE AUTHOR'S SUMMARY.

ACTION OF VITAMIN K ON "HEMOPHILUS PERTUSSIS." A. SAYOA LOBATO and ORESTE CARVALHO, Presse méd. Supp. 20, p. 421 (March 17) 1954.

Reports from a number of investigators on the favorable effect of vitamin K in whooping cough have prompted the authors to assess in vitro the eventual bacteriostatic and bactericide potency of this vitamin with regard to Hemophilus pertussis and thus to attempt some explanation for its mechanism of action.

Results, as tabulated in this paper, show that the blood of those subjects who had been given vitamin K possesses a marked bacteriostatic action on Hemophilus pertussis and that the action increases in relation to the augmentation of the doses. On the other hand, it was observed that such a bacteriostatic action was not present in the blood of the subjects prior to administration of vitamin K.

Another significant point is that a solution made up of this vitamin does not show any bacteriostatic action on Hemophilus pertussis.

FROM THE AUTHORS' SUMMARY.

POLIOMYELITIS IN NORTH VIETNAM (AN EPIDEMIC AT HANOI, MARCH-JUNE 1950). RIVAOLEN, TRINH NCOC PHAN, and NGUYEN DUC QUANG, Presse méd. Supp. 65, p. 1314 (Oct. 14) 1953.

An epidemic of acute poliomyelitis anterior broke out in Tonkin Delta during March, April, May, and June, 1950. It was the first epidemic of this condition so far observed in Annam. With respect to the town Hanoi, 297 cases were reported to the board of health, but there seemed to be, in reality, five times as many cases. Children under 5 years of age were affected in a proportion of 85%, with a mortality rate of 8.62% as noted among the hospital in-patients, that is, among those most severely affected.

The epidemic developed before the warmest season, reversing what is observed in those other countries where the disease generally corresponds to the hot weather period. On the other hand, it coincided with maximum lowering of the water table, which lowering was more marked in 1950 as a consequence of relative drought during the winter.

The epidemic was localized in the overcrowded parts of the town where the hygienic conditions were very poor and usually centers of digestive epidemics.

FROM THE AUTHORS' SUMMARY.

THE SUBCUTANEOUS SMALLPOX VACCINATION. K. BERGER, Schweiz. med. Wchnschr. **84**:33 (Jan. 9) 1954.

The advantages and disadvantages of subcutaneous smallpox vaccination are discussed and contrasted with those of cutaneous vaccination. It is concluded that at present subcutaneous vaccination is to be recommended only in selected cases.

AMBERG, Rochester, Minn.

TREATMENT OF CERTAIN INFECTIOUS DISEASES WITH HUMAN SERUMS. R. MARTIN DU PAN and L. RAZA, Schweiz. med. Wchnschr. **84**:271 (Feb. 27) 1954.

The effect of convalescent human serum or gamma globulin in the prevention or attenuation of measles is discussed, as well as that of convalescent serum for mumps. The hyperimmune serum treatment of whooping cough has proved quite satisfactory.

AMBERG, Rochester, Minn.

TREATMENT OF POLIOMYELITIS WITH HIGH DOSAGE OF ASCORBIC ACID. O. GSELL and F. KALT, Schweiz. med. Wchnschr. **84**:661 (June 12) 1954.

The treatment of patients with poliomyelitis with large doses of ascorbic acid did not have any beneficial effect.

AMBERG, Rochester, Minn.

THE SENSITIVITY OF LOEFFLER'S BACILLUS TO DIFFERENT ANTIBIOTICS. C. CASCIO and R. PURPURA, Clin. pediat. **35**:747 (Oct.) 1953.

Tests were made to determine the sensitivity of 60 strains of Corynebacterium diphtheriae to six different antibiotics. The more virulent strains of the C. diphtheriae required greater concentrations of penicillin, oxytetracycline (Terramycin) and tyrothricin for bacteriostasis than did the less virulent strains. This was not the case with chloramphenicol (Chloromycetin), streptomycin, or chlortetracycline (Aureomycin).

HIGGINS, Boston.

VACCINATION AND ACUTE ANTERIOR POLIOMYELITIS. W. TANGHERONI and G. MENICHINI, Minerva pediat. **5**:1048 (Nov. 30) 1953.

Five cases are reported of children who developed acute poliomyelitis shortly after they had received a routine prophylactic injection. Four of the children had been given an injection of alum-precipitated diphtheria toxoid, and one child an injection of pertussis vaccine. Each child

developed some paralysis, which was most marked in the arm or leg into which the prophylactic injection had been given. The time from injection to the onset of the poliomeylitis was 3, 5, 16, 18, and 28 days, respectively. The suggestion is made that when poliomyelitis is prevalent, prophylactic injections be postponed until the epidemic is past.

HIGGINS, Boston.

CHLORTETRACYCLINE (AUREOMYCIN) IN THE TREATMENT OF PERTUSSIS. G. POLI and W. FURNAGALLI, Minerva pediat. **6**:149 (March 15) 1954.

Twenty-six children with uncomplicated pertussis were given 15 to 20 mg. per kilogram of body weight of chlortetracycline (Aureomycin) daily. In two cases, the cure was "dramatic," or within 2 days; in five cases the cure was complete in 8 to 10 days; in seven cases, the coughing continued after 10 days, but was no longer paroxysmal. Of the other 12 cases, 8 showed some reduction in the number of paroxysms, while the course of the other 4 cases seemed unaffected by the medication.

HIGGINS, Boston.

Acute Infectious Diseases

INTESTINAL OBSTRUCTION DUE TO ASCARIASIS. MARGARET Q. JENKINS and M. W. BEACH, Pediatrics **13**:419 (May) 1954.

The authors discuss 31 patients with obstruction of the small intestine due to Ascaris, with two deaths. These patients were seen during a five-year period.

Treatment consisted of Wangensteen suction, parenteral fluids, and small doses of hexylresorcinol crystoids without a laxative, given for several days, or of Hetrazan, 6 mg. per kilogram of body weight, three times daily for one week.

Obstruction was relieved, and no evidence of toxicity occurred.

FROM THE AUTHORS' SUMMARY.

ANEMIA IN CHILDREN WITH ENTERIC FEVER. S. T. WINTER and H. SALOMON, Ann. pædiat. **182**:241 (April) 1954.

Five children with typhoid fever and one with paratyphoid fever showed a severe anemia with reticulocytosis. In one case the serum bilirubin was raised, and in five the bone marrow showed an increased erythropoiesis. The etiology of this anemia is discussed, and the possibility of a hemolytic process is noted.

FROM THE AUTHORS' SUMMARY.

RELAPSES IN TYPHOID FEVER TREATED WITH CHLORAMPHENICOL (CHLOROMYCETIN). JULIO MENEGHELLO, OSCAR UNDURRAGA A, and ALFREDO MAIMANN, Rev. chilena pediat. **25**:119 (March) 1954.

The relapse of the typhoid fever treated with chloramphenicol (Chloromycetin) is of relatively frequent observation, 8.9% in the authors' material. Relapse occurred in an average time of 16 days after return to normal temperature. The relapses presented were preferable in those cases in which typhoid fever had dangerous evolution.

The clinical symptomatology was similar to that of the typhoid fever, but in general less severe. The reactions of agglutination showed tendency to remain positive or increase their titer. In only three cases during the relapse were they negative. In seven, relapses a positive culture of the blood was made, in four, positive culture of the feces, and in three, positive culture of the urine. The blood picture in the majority of the patients presented characteristics similar to that of the typhoid fever.

No increase in the frequency of the relapses was observed with the reduction of the treatment of chloramphenicol for 10 days. Out of the total of 30 relapses, 5 presented complications, some dangerous and even mortal on one occasion. The appearance of relapses was not foreseen with the practice of the antityphoid vaccination which we made systematically in all our patients once the temperature was normal. The treatment was practiced in 20 patients with the same doses of chloramphenicol and for the same length of time as in typhoid fever, and, due to the number of relapses which showed complications, a treatment with chloramphenicol is advisable.

FROM THE AUTHORS' SUMMARY.

RABIES IN A CHILD WITH AN INCUBATION PERIOD OF EIGHT MONTHS. L. POTENZA and M. C. MARANTE, Arch. venez. puericult. pediat. **16**:221 (April-June) 1954.

A case of rabies in a 3-year-5-month-old male child is described. The patient had not received antirabies vaccination. The incubation period was eight months. The diagnosis was made by histological examination of the nervous system and by intracerebral inoculation in the mouse.

FROM THE AUTHORS' SUMMARY.

THE PROBLEM OF THE ENDOGENOUS MYCOSIS. CHRISTOF WUNDERLICH, Deutsche med. Wchnschr. **78**:1736 (Dec. 11) 1953.

The lungs and kidneys of a large number of children (the exact number is not given) who had died of a variety of diseases were examined for the presence of Candida albicans, which was found in 60% of cases. Negative results were obtained in older children and in very young premature infants who had survived only a few hours or days. Yeast could be grown from the catheterized urine of severely ill, mainly male, infants without clinical evidence of an endogenous mycosis. An ascending infection is regarded as very improbable. With improvement in the general condition, the organisms disappeared. A few cases of infants are given where an apparently innocuous respiratory tract infection with a sudden severe exacerbation ended fatally. In the thick mucoid material of the bronchial system, a type of Candida albicans was found on microscopy and by culture. The buccal cavity was the seat of extensive thrush. Examples of extensive Candida invasions resulting from antibiotic treatment are cited.

AMBERG, Rochester, Minn.

THE INCIDENCE OF INTESTINAL PARASITES IN CHILDREN OF A MID-SLOVAKIAN DISTRICT. Z. CICVAREK, P. MYSKA, and D. MYSKOVA, Pediat. listy **8**:34, 1953.

The examination of 1,000 stools revealed that 34% of children of the mid-Slovakian district of Hnusta are carriers of intestinal parasites.

FROM THE AUTHORS' SUMMARY.

Chronic Infectious Diseases

TOXICITY OF ISONICOTINIC ACID HYDRAZIDES IN PULMONARY TUBERCULOSIS: TOXICITY OF ISONIAZID AND IPRONIAZID USED ALONE AND IN COMBINATION WITH STREPTOMYCIN OR *p*-AMINOSALICYLIC ACID. E. O. COATES JR, G. L. BRICKMAN, and G. M. MEADE, A. M. A. Arch. Int. Med. **93**:541 (April) 1954.

The authors review their experience in treating 42 patients on various treatment schedules of iproniazid, isoniazid, streptomycin, and *p*-aminosalicylic acid (PAS). Iproniazid, while apparently more effective than isoniazid, is considered too toxic for general use. Potentially serious effects include mental changes, peripheral neuropathy, severe muscular spasms, and hemolysis. Nine percent of the patients receiving isoniazid had minor side effects, but this drug is considered a safe drug for therapeutic use.

JONES, Chicago.

TREATMENT OF TUBERCULOUS MENINIGTIS IN CHILDREN. E. L. KENDIG JR., R. OWNBY JR., G. E. TREVATHAN, and L. E. SUTTON, J. Pediat. **43**:532 (Nov.) 1953.

The authors report 40 cases of tuberculous meningitis in children treated with streptomycin, intramuscular and intrathecal. Some of these patients were given thiazolsulfone (Promizole), paraaminosalicylic acid (PAS), and isoniazid.

The survival rate was 45%. Mortality rate was higher in the Negro children in this series. Children with x-ray evidence of miliary tuberculosis had a poor prognosis. Isoniazid appeared to be helpful in the treatment. It was used with streptomycin and PAS in only seven patients. The small number of patients in this review defies a critical analysis.

MACDONALD, Pittsburgh.

ISOLATION OF HISTOPLASMA CAPSULATUM FROM THE AIR. MARTHA J. IBACH, H. W. LARSH, and M. L. FURCOLOW, Science **119**:71 (Jan. 8) 1954.

The authors report the isolation of the organism Histoplasma capsulatum from the air of two chicken houses located in Kansas and Missouri, respectively. Organisms were also recovered from debris within the buildings and from the soil just outside. In each instance, evidences of pulmonary histoplasmosis were found in humans who had worked in these buildings.

FORBES, Rochester, N. Y.

ECTOPIC OSSIFICATION IN TUBERCULOUS MENINGITIS. JOHN LORBER, Arch. Dis. Childhood **28**:98 (April) 1953.

Ectopic ossification was demonstrated radiologically in 5 of 10 children who developed temporary paraplegia in flexion during streptomycin treatment of tuberculous meningitis and survived for more than three months. It was found two to six months after the onset of the paraplegia. In all cases, the ossification affected the iliopsoas or the abductors of the thighs and their tendons below the level of the pelvis. The lesions were bilateral in three patients. They led to severe symptoms in the others. Operative removal of the new bone in one child led to more extensive deposition of new bone and a worsening of his condition. In two conservatively treated patients, there was subsequent radiological evidence of spontaneous absorption of new bone after recovery from meningitis.

The diagnosis was established radiologically in all patients and was confirmed at operation in one and at necropsy in another child. Histologically the ectopic tissue appeared to be normal bone with bone marrow.

The incidence and nature of neurogenic metastatic ossification was reviewed. No previous instances in association with tuberculous meningitis have been found.

KELLY, Milwaukee.

ACTINOMYCOSIS OF THE CHEST WALL, N. J. ROTHFIELD, Proc. Roy. Soc. Med. **47**:127 (Feb.) 1954.

Actinomycosis of the chest wall in a 9-year-old boy is discussed. After five months of treatment, Actinomyces was still present in the abscess.

McGUIGAN, Evanston, Ill.

TOXOPLASMA ENCEPHALITIS IN SOUTH AFRICA. B. J. P. BECKER, South African M. A. J. **28**:21 (Jan.) 1954.

Two cases of fatal toxoplasma encephalitis are described. The first was congenital, occurring in an infant who developed hydrocephalus at 3 weeks of age and died at 5 months of age. The other was a 4½-year-old girl with fulminating encephalomyelitic symptoms following a two-month period of minor malaise.

McGUIGAN, Evanston, Ill.

PRECISE INDICATIONS FOR THE READING AND INTERPRETATION OF A BCG VACCINATION. MAX FOURESTIER, Presse méd., Supp. 5, p. 81 (Jan. 23) 1954.

At the very time when BCG vaccination is being enforced, the author thinks it useful to provide the practitioners with precise indications on such information as is now available from the reading of the skin vaccinal reaction induced by scarification and from the reading of the control tuberculin tests.

Study of the reading is presented as follows: (1) Reading on the seventh day. (2) Reading on the 20th day including (*a*) negative reaction, (*b*) skin reaction of middle intensity, (*c*) skin reaction very strongly positive. (3) Reading on the second month including (*a*) reaction remaining negative, (*b*) reaction showing moderately positive, (*c*) reaction showing very strongly positive. (4) Interpretation on the sixth month. (5) Allergoimmune interpretation during the years following BCG scarifications (in a subject whose conditions of vaccination and progress of the two-month period following vaccination are ignored).

FROM THE AUTHOR'S SUMMARY.

ENCEPHALOGRAPHIC FINDINGS IN CHILDREN WITH TUBERCULOUS MENINGITIS. C. IMPERATO, Lattante **25**:193 (April) 1954.

Encephalography affords an important criterion as to the prognosis and the clinical progress of patients with tuberculous meningitis. Repeated tracings are desirable as treatment progresses. Diffuse reduction of the cerebral electrical activity is the usual characteristic of the disease. The electrical activity increases with a favorable evolution of the disease. Localized foci of encephalitis may frequently be spotted and their progress followed. A surer evaluation of a cure is established by encephalography.

HIGGINS, Boston.

TUBERCULIN PATCH TESTS. E. TAUBER, Minerva pediat. **5**:864 (Oct. 15) 1953.

Comparative tuberculin tests by the patch and the intradermal methods were done on 125 children. The data revealed results so similar by each method that the conclusion was drawn that the patch test is reliable diagnostically, as well as being easier to give and less disturbing to the patient.

HIGGINS, Boston.

THE MECHANISM OF THE ACTION OF PARAAMINOSALICYLIC ACID. E. BOTTONE and C. CIPOLLONI, Minerva pediat. **5**:870 (Oct. 15) 1953.

Twenty children, some of them healthy and others with tuberculosis, were given paraaminosalicylic acid (PAS), either orally or intramuscularly. In each case, there was a diminution in the number of eosinophilic blood cells and an increase in the uric acid: creatinine ratio in the urine. The conclusion was reached that PAS, probably indirectly, stimulated the adrenal glands.

HIGGINS, Boston.

HYDROCEPHALUS IN TUBERCULOUS MENINGITIS. A. SCHIAVINI, Minerva pediat. **5**:874 (Oct. 15) 1953.

Between April, 1948, and September, 1952, 100 patients with tuberculous meningitis have been treated at the Ospedale Maggiore della Carita, in Novara. Forty of the 70 children (57%) and 9 of the 30 adults (30%) have been cured. Twenty-five of the 100 patients have had a hydrocephalus, which, however, was of a varying degree in the individual cases. Each of these 25 patients was being given streptomycin. The degree of hydrocephalus varied according to whether or not there were block or encephalographic changes, or only a persistent high spinal fluid pressure or definite changes traceable to meningeal adhesions.

HIGGINS, Boston.

OSTEOARTICULAR TUBERCULOSIS TREATED WITH ISONIAZID. EUGENIO DIAZ and MARION GONZALEZ, Rev. chilena pediat. **25**:81 (Feb.) 1954.

The results obtained in 14 children with osteoarticular tuberculosis of diverse localizations treated with isoniazid and controlled for more than one year are detailed. The drug was given by mouth in doses of 10 mg. per kilogram of body weight per day during the first six months and 5 mg. per kilogram of body weight per day in the six months that followed. Locally it was only used in one case in a solution of 25 mg. per cubic centimeter of saline solution. No other medical or surgical treatment was used. The general and local results were very satisfactory in all cases. There was considerable improvement in the nutritional status and a quick decline of the tuberculous toxemic manifestations. Locally, a rapid action was observed on the pains and the healing of abscesses and fistulas in a period of less than 45 days. X-rays showed a detention of the destructive processes with a quick tendency to healing of the bone.

FROM THE AUTHORS' SUMMARY.

Diseases of Blood, Heart and Blood Vessels, and Spleen

ACUTE LEUKEMIA IN TWINS. JEAN V. COOKE, J. A. M. A. **152**:1029 (July 11) 1953.

The case of fraternal twins who died from acute leukemia at the ages of 18 and 24 months is reported. Familial leukemia, except in twins, is an extreme rarity.

KIMBALL, Evanston, Ill.

KUNDRAT'S LYMPHOSARCOMA EVOLVING INTO ACUTE LEUKEMIA. ALBERTO FOIS, Riv. clin. pediat. **51**:41 (Jan.) 1953.

The author reports a case of Kundrat's lymphosarcoma which evolved into acute leukemia. The nosologic situation of the disease is briefly discussed, and the resemblance to acute leukemia is pointed out.

FROM THE AUTHOR'S SUMMARY.

INORGANIC PHOSPHATE IN BLOOD SERUM. JOSÉ AVELINO CARTAYA, BERTHA LUISA DE MAJO, and GERMAN LARA, Arch. venezol. puericult. y pediat. **15**:349 (Oct.-Dec.) 1952.

The different changes in serum inorganic phosphate were studied in 50 children up to 8 years of age, clinically normal, in fasting state and after the ingestion of disodium phosphate.

An increase over the fasting level was observed in the first, second, and third hours after the ingestion of the test dose. The following results were obtained, expressed as the difference between the fasting level and the level after the test dose: after the first hour, 1.98 mg. per 100 cc. $\pm$ 0.82; at the second hour, 2.42 mg. per 100 cc. $\pm$ 1.043; at the third hour, 1.82 mg. per 100 cc. $\pm$ 0.89.

The serum inorganic phosphate state of the 50 children ranged between 3.10 and 5.30 mg. per 100 cc., with an average of 4.16 $\pm$ 0.4 (standard error 0.056).

According to our results, the test could be simplified without losing any of its value by using only the fasting level and the first hour determination.

FROM THE AUTHORS' SUMMARY.

SEVERE HYPOCHROMIC MICROCYTIC ANEMIA WITH SPLENOMEGALY IN A CHILD OF SEVEN YEARS. C. J. VAN WISSELINGHI and CHARLOTTE DE KRUIJFF, Maandschr. kindergeneesk. **21**:128 (April) 1953.

A case of severe hypochromic microcytic anemia with splenomegaly and achylia gastrica in a boy 7 years old is described. For three years the patient had repeatedly eaten lead paint, and for a long time he had been suffering from malnutrition.

The difference between increased lead absorption and lead poisoning is discussed. This patient showed no symptoms of lead poisoning. The authors stress the fact that such paint also contains other poisonous components which could have caused the symptoms. Finally, the connection between achylia gastrica and hypochromic anemia and other causes of pica is discussed.

FROM THE AUTHORS' SUMMARY.

Diseases of Lungs, Pleura, and Mediastinum

MILK-ASPIRATION PNEUMONIA IN HUMAN AND ANIMAL SUBJECTS. THOMAS J. MORAN, A. M. A. Arch. Path. **55**:286 (April) 1953.

Pneumonia caused by aspiration of milk, usually classified as a form of lipid pneumonia, is a recognized complication in pediatric practice. The clinical diagnosis is difficult. A history of difficulty in swallowing, choking during feedings or gavage feedings in infants, especially in regard to premature infants, may often be obtained. There is clinically a resistence to antibiotic therapy. Otherwise, the clinical features of milk-aspiration pneumonia are essentially those of a pneumonia caused by other agents. At autopsy the gross diagnosis of milk-aspiration pneumonia cannot be made unless the process is acute and milk is found in the bronchi. The trachea should be tied before the lungs are removed if aspiration of milk seems likely. When milky fluid is found, smears of the material should be stained with Sudan IV for fat globules. The affected lung will show a bronchopneumonia, often hemorrhagic and often associated with areas of emphysema. The dependent portions are most widely involved, as is true in other forms of aspiration pneumonia. Occasionally abscesses are found in the lungs, showing a lobar type of pneumonia. The microscopic features are characterized by widespread granulomas, alveolar thickening, giant-cell reaction, fibrosis, abscess formation, and an acute pneumonia. The reaction is usually mononuclear. The author found experimentally in rabbits that the tissue reactions to feeding mixtures, human milk, and cow's milk evolved a similar reaction as seen in human milk aspiration. However, the immediate reaction to large amounts (10 cc. or more) of feeding mixture is entirely different from the reaction to identical amounts of cow's milk or human milk. Relatively small quantities of feeding mixture often produced death from pulmonary edema in 1 to 11 minutes, while similar quantities of cow's or human milk rarely caused death.

Although some features of the disease both in human and animal lungs resembled the pneumonias of liquid petrolatum or cod-liver oil, the general reaction more closely resembles that seen in response to injection of solid foods. Because the response is to milk protein as well as to the fat, the term milk-aspiration pneumonia appears more apt to the author.

CHAN, San Francisco.

CLINICAL REMARKS ON ATYPICAL PNEUMONIA IN CHILDHOOD. J. HOUSTEK and V. MYDLIL, Pediat. listy **8**:183, 1953.

A clinical survey of the cases described in detail pathologically is given. Three types are described according to the course of the disease:

1. An acute grave illness with hyperpyrexia, bronchiolitis, or a grave toxic state with alteration of the sensorium, convulsions, and dyspnea leading to death, usually within 24 hours from admission. These pneumonias belong mostly to the Adams' type of pneumonia or to a combination of Adams' type and the large cell type, or the Adams' and Jersild's type.

2. The course of the disease is somewhat prolonged; some children had no fever or any pronounced signs indicative of a disease of the respiratory system; other children had signs of pneumonia of considerable duration. Histologically, they were confirmed as large cell pneumonia, primary atypical, and postmeasles pneumonia.

3. The disease manifests itself as a progressive disease of the lung, without fever, with pronounced pulmonary symptoms, and with signs of hypertrophy of the right side of the heart, as a chronic interstitial pulmonary fibrosis.

FROM THE AUTHORS' SUMMARY.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

EOSINOPHILIA-HEPATOMEGALY SYNDROME OF INFANTS AND YOUNG CHILDREN. CONN L. MILBURN JR. and KENNETH F. ERNST, Pediatrics **11**:358 (April) 1953.

Attention is directed to the existence of a recently recognized syndrome in infants and young children with the prominent features of chronic eosinophilia hepatomegaly, liver biopsy findings of eosinophilic infiltrative and granulomatous lesions, a benign course, and, occasionally, symptoms and signs of transient pneumonitis.

An analysis of 15 reported cases of the syndrome is presented, including the report of a case due to an unidentified nematode larva, probably Toxocara canis, invading the liver.

Signs and symptoms, pathology, pathogenesis, etiology, course and prognosis, and treatment are discussed.

Evidence is preponderantly in favor of the etiology in all cases being nematode larvae invasions of the liver and other viscera.

These cases cause conjecture as to whether other diseases of chronic eosinophilia, such as Löffler's syndrome, tropical eosinophilia, familial eosinophilia, pseudoleukemic eosinophilia, etc., may not also be due to visceral nematode larvae migrations. Further investigation is warranted in these diseases.

FROM THE AUTHORS' SUMMARY.

SUBPHRENIC ABCESS AND UMBILICAL FISTULA IN AN INFANT. J. F. R. BENTLEY, Great Ormond St. J. (No. 6) p. 113, Dec., 1953.

An infant with fever of obscure origin was found to have a subphrenic abcess. An umbilical sinus followed by a fecal fistula developed, and it is felt that the primary pathology may have been an infected omphalomesenteric cyst.

MCGUIGAN, Evanston, Ill.

WATER INTOXICATION: A HAZARD IN MEGACOLON. J. L. Potts, Clin. Rep. Adelaide Child. Hosp. **2**:141 (May-Nov.) 1953.

Two cases of water intoxication are reported, and the dangers of enemas in megacolon are stressed. Disturbances include low sodium shock with cerebral edema. Treatment is early administration of hypertonic saline intravenously.

MCGUIGAN, Evanston, Ill.

OPERATIONS ON CONGENITAL INTESTINAL OBSTRUCTIONS IN THE NEWBORN. B. TARACENA DEL PIÑAL, L. GONZÁLEZ-COVIELLA, L. SERRADA, and B. CADARSO, Acta pediát. españ. **11**:808 (Sept.) 1953.

The authors present the clinical history, preoperation care, x-rays, and operation procedure used on two newborn infants who had intestinal anomalies. One infant was 3 days old and the other 4 days old when brought to the hospital. Both followed the classic descriptions of congenital microcolon, but there existed other anomalies not compatible with life.

Both babies died, and autopsy showed not only congenital microcolon, but also, in the case of the second child, atresia of the ureters and hydronephrosis. ALLEN, Santa Fe, N. Mex.

Nervous Diseases

BRACHIAL PLEXUS INJURIES. DONALD S. MILLER, WILLIAM F. LICHTMAN, and ROY O. SEBECK, Illinois M. J. **103**:299-304 (May) 1953.

Brachial plexus lesions occasionally occur with dislocations of the shoulder joint, fractures of the shoulder, or clavicular injuries. Early treatment is imperative and should consist of immediate reduction of the shoulder joint and a careful evaluation of the peripheral nerves. Reexamination is imperative, and good records are important to determine the progress of the condition. Brachial plexus lesions should be treated by careful abduction splinting, galvanic muscle stimulation, and active and passive motion of the joints. In the presence of severe neurovascular complications or those cases associated with severe trophic disturbances, amputation may be necessary. Before amputation, every consideration should be given regarding the possibility of joint reconstruction or fusion operations. Prophylactically, doors of automobiles should be carefully locked in order to avoid injuries to children such as are described above.

FROM THE AUTHORS' SUMMARY.

POTASSIUM AND TETANY. G. FANCONI and T. NEUHAUS, Helvet. pædiat. acta **8**:424 (Nov.) 1953.

After a critical review of the literature dealing with potassium in relation to the excitability of nerves, the authors report their own observations confirming this relationship.

In several cases of pseudo uremic eclampsia the kidney deficiency caused K retention in the extracellular fluid, and this retention favored, or even induced cramps.

Neonatal tetany is probably due to a transitory or persistent underfunction of the parathyroid glands, as well as to the inability of the kidney of the newborn to excrete an increased amount of phosphate. The frequent finding of an absolute or relative (in relation to Ca) hyperkalemia seems to favor cramps.

In toxic dehydration, hyperkalemia, which may appear only after the intravenous use of K-containing solutions, may likewise favor cramps.

Frequently, they found in older children with labile autonomic nervous systems and normocalcemia that tetany raised the level of K, but only moderately so.

FROM THE AUTHORS' SUMMARY.

PURULENT MENINGITIS IN COURSE OF TREATMENT OF TUBERCULOUS MENINGITIS. D. GOTTI, Clin. pediat. **35**:898 (Dec.) 1953.

Of 219 patients undergoing treatment for tuberculous meningitis by streptomycin, 19 developed secondary purulent meningitis; 16 of the cases occurred after the second month of treatment. Three patients died of the purulent infection, and four others, of their tuberculous infection. A high fever and meningeal symptoms permitted an early diagnosis, so that treatment by suitable antibiotics could be started immediately. Improper puncture technique could be ruled out as the etiological factor in many of the cases. A respiratory infection or a sore throat frequently preceded the meningitis. In two cases the patients were not receiving intrathecal injections at the time of the onset of the purulent meningitis. HIGGINS, Boston.

HYDATID CYST OF THE BRAIN. ROMÁN ARANA IÑIGUEZ, J. SAN JULIÁN, AGUSTÍN GORLERO ARMAS, and BLLER. BARTÒLOMÉ FUSTER, Arch. pediat. Uruguay **24**:631 (Oct.) 1953.

Observations in four cases of hydatid cyst of the brain are reported. In three cases the diagnosis was made by angiography. The authors believe that this procedure is the best one for localization and etiological diagnosis. The angiographic appearance is often pathognomonic of this cerebral parasitosis.

The four patients were successfully treated. The first patient was operated on by the method proposed by A. H. Schroeder, two by E. Dowling's method, and the fourth by the procedure proposed by Arana Iñiguez, Rodríquez Barrios, and San Julián. The authors believe that this method is the most advantageous.

FROM THE AUTHORS' SUMMARY.

Psychology and Psychiatry

DEVELOPMENTAL TRENDS IN ABSTRACTION ABILITY OF CHILDREN. IRVING E. SIGEL, Child Developm. **24**:131 (June) 1953.

Sixty white lower-middle-class children, 20 each from the age groups of 7, 9, and 11 years, who were in the correct grades for their age and whose percentile rank scores on the Progressive Matrices test (Raven) ranged from the 25th to 75th percentile, were selected as subjects. To each child, five test situations, each containing 24 familiar toy objects, pictures of these toys, and word names of the toys, were presented. They were instructed to group materials on the basis of similiarity.

The data presented reveal a decrease with age in perceptual classification of items. This decrease was significant between the ages of 7 and 9 years, but not between the ages of 9 and 11 years, when children were asked to reduce groupings. The use of conceptual classifications increased steadily with age. Placement of items in miscellaneous categories was negatively correlated with age when the children were allowed free choice of grouping, but when urged to reduce the number of groupings, an age trend was not found.

Seven-year-old children principally used groupings of the thematic type in their first trials and repeated that approach when requested to reduce the number of groupings.

Nine-year-old children tended to use conceptual and perceptual classifications equally and made some use of the miscellaneous categories as well. When requested to reduce the number of groupings, they increased perceptual and miscellaneous classifications and reduced conceptual groupings.

Eleven-year-old children employed conceptual groupings predominantly but used the perceptual approach about as frequently as did 9-year-old youngsters. Miscellaneous classifications were infrequent when grouping was spontaneous. With pressure to reduce the number of groupings, conceptual and perceptual classifications still were used, but recourse to the miscellaneous category increased.

When groupings of the objects were made by the experimenter, the children's efforts to identify the bases he had in mind did not reveal essentially different patterns of thought than did the groupings made by the children themselves.

FROM THE AUTHOR'S SUMMARY.

CONVERGENCE: AN ACCELERATED LONGITUDINAL APPROACH. RICHARD Q. BELL, Child Developm. **24**:145 (June) 1953.

The convergence approach appears to have greatest utility in two types of situations: (*a*) in investigations basically oriented toward a cross sectional approach, in which there is reason for concern over the comparability of the experimental groups relative to the dependent variable on factors other than age and in which it is possible to make limited remeasurements of these groups, and (*b*) for investigations oriented toward the longitudinal approach but faced with problems of transient or less cooperative groups or with possibilities of undesirable contamination of the experimental population by extensive observation.

It is expected that the desire to anticipate long-term trends as early as possible and the need to incorporate current research developments would favor the use of the cross sectional and convergence approaches. The desire to follow individual changes, when reformulated, as the desire to identify and follow statistically meaningful sub-groups, does not preclude the use of the convergence approach. If the cumulative effect of an independent variable on a single person is to be studied, however, the convergence and cross sectional approaches cannot be used.

FROM THE AUTHOR'S SUMMARY.

THALAMIC PATHOLOGY OF AMAUROTIC FAMILY IDIOCY: CONTRIBUTION TO THE CYTOLOGY OF THE THALAMUS. L. H. LEMIEUX, J. Neuropath. & Exper. Neurol. **13**:343 (April) 1954.

Lemieux reports studies on the pathology of the optic thalami in two cases of amaurotic family idiocy which occurred in identical twins, beginning at the age of 4 years and lasting for five years. The typical nerve cell changes, with marked swelling of the nerve cells, with displacement of the nucleus and partial to complete tigrolysis, and with much abnormal lipoidal material within the cytoplasm are recalled. From the cytologic investigation it appeared that the intralaminar nuclear system appeared to be more diffuse than is generally realized. The nuclei with subcortical connections are composed of neurons of a single type, none of which showed vacuolar changes. Of the cortical relay nuclei, the anterior nucleus contained only vacuolated neurons and small nerve cells; the ventral nuclei, exclusive of the anteroventral nucleus, contained three types of nerve cells with few vacuolated neurons. All the association nuclei showed vacuolar changes and some loss of nerve cells. Many of the thalamic nuclei contained a distinct type of small neuron which is not found in the intralaminar system, the midline nuclei, the reticular nucleus, and the medial and lateral geniculate bodies. In general, the neurons of the centromedian nucleus were less affected than those of the anterior medial and lateral nuclei, in which the neurons were fewer in number and contained giant vacuoles with large lipoidal inclusions.

SIEKERT, Rochester, Minn. [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

Diseases of Genitourinary Tract

THE EFFECT OF PROLONGED LOCAL TREATMENT WITH ADRENOCORTICAL AND SEX STEROIDS ON THE INTRADERMAL SPREADING ACTION OF HYALURONIDASE. MARK A. HAYES, Endocrinology **52**:646 (June) 1953.

The inhibition of hyaluronidase activity as it affects the dermal spreading of an indicator substance by an acutely elevated blood level of either endogenously or exogenously supplied adrenocortical steroids has been confirmed.

This report deals with an extension of previous studies, as related to specific pure crystalline steroids.

It was found that prolonged local application of corticosterone or testosterone does not influence the spreading action of hyaluronidase. Similar treatment with estrogen produces a profound systemic effect and accentuates hyaluronidase spreading, but only in the rapid phase. On the contrary, 17-hydroxycorticosterone produces an effect restricted to the area of treatment characteristic of adrenocortical steroids, that is an accentuated rate of spreading and nearly complete abolition of the slow phase.

JACOBSEN, Buffalo.

THE EFFECT OF HYPOPHYSECTOMY ON FETAL AND PLACENTAL GROWTH IN THE RAT. ERNEST KNOBIL and WILLIAM L. CATON, Endocrinology **53**:198 (Aug.) 1953.

Hypophysectomy of pregnant rats on the 12th day of gestation effected a highly significant decrease in fetal weight and a lesser decrease in placental weight than when these were determined on the 21st day of gestation.

JACOBSEN, Buffalo.

GLYCOGEN DEPOSITION IN DIFFERENT SKELETAL MUSCLES INDUCED BY CORTISONE AND ESTRADIOL. SAMUEL L. LEONARD, Endocrinology **53**:226 (Aug.) 1953.

The results reported show that cortisone was able to increase the glycogen level in some skeletal muscles but not in others.

JACOBSEN, Buffalo.

EFFECT OF ACTH ON RESPONSIVENESS TO INSULIN. H. J. ZIMMERMAN, A. E. PARRISH, and L. K. ALPERT, Metabolism **2**:424 (Sept.) 1953.

The glucose-insulin test of Himsworth was carried out on 17 patients suffering from various diseases. After a course of corticotropin (ACTH) administered to each patient, the test was repeated, and it was found that in only four was there any loss of insulin sensitivity. These observations were unexpected in view of several previous demonstrations that adrenal cortex hormones exerted "diabetogenic" or anti-insulin effects. In patients with diabetes mellitus, for example, it has been reported that the administration of corticotropin or cortisone increases the severity of the disease and increases the insulin requirements.

KAPLAN, New York.

THE IMPORTANT ROLE OF THE SUPRARENAL CORTEX IN THE PATHOGENESIS OF THE SYNDROME OF DECHLORINATION IN HABITUAL VOMITING IN DYSTROPHIC INFANTS. E. CHELI and O. OLIVI, Clin. pediat. **35**:471 (July) 1953.

A premature infant had done well clinically and gained weight until she was 4 months old. During the next seven months, she had not gained any weight and had had frequent severe episodes of vomiting. A study of the dystrophic infant revealed hypochloremia and nonrenal hyperazotemia; no gastrointestinal pathology was detected by x-ray examination. Injections of cortisone and saline infusions proved of no clinical benefit, but when injections of desoxycorticosterone were also given, the vomiting ceased, the blood chemistry became normal, and the child gained in weight. It would appear that the basis of the syndrome presented by this infant was in the salt-regulating mechanism of the suprarenal cortex.

HIGGINS, Boston.

EFFECT OF CORTICOTROPIN ON EXCRETION OF 17-KETOSTEROIDS AND OF 11-OXYCORTICOSTEROIDS AND ON BLOOD COUNTS IN INFANTS. B. CARLETTI and A. DE BARBIERI, Minerva pediat. **5**:1067 (Dec. 15) 1953.

Eight small infants, from 1 to 20 months of age, were given corticotropin (2 units per kilogram) for three days. There was an immediate and parallel increase in the daily excretion of the 17-ketosteroids and the 11-oxycorticosteroids and of nitrogen and uric acid. Two days after the corticotropin injections had been discontinued, the excretion of these products had fallen to the premedication levels. The blood eosinophile counts fell during the medication, as is the case with adults.

HIGGINS, Boston.

CASE OF PRECOCIOUS PUBERTY, PROBABLY DUE TO DIENCEPHALIC TUMOR. G. COTELLESSA and F. DE MATTEIS, Minerva pediat. **5**:1084 (Dec. 15) 1953.

A 7-year-old boy presented the findings of gigantism and precocious puberty. For three years he had been subject to convulsive seizures. His blood pressure was 95/50, and there were no signs of increased intracranial pressure. A careful diagnostic study was made, including pneumoperitoneal roentgenograms, pneumoencephalograms, and electroencephalograms. The probable diagnosis was a slowly growing brain tumor localized somewhat to the left of the posterior clinoid process. Exploratory surgery was being considered.

HIGGINS, Boston.

GROWTH OF ALBINO RATS AFTER TOTAL REMOVAL OF THYMUS GLAND. M. POZZAN, Minerva pediat. **5**:1104 (Dec. 15) 1953.

The thymus glands were removed from 20 white rats, 8 to 10 days old; that the ablation was total was later proved in 5 of the rats by a histological examination of serial sections of the neck and thorax. Twenty other white rats of the same age, serving as control animals, had a sternopleurotomy.

There was no indication that thymectomy affected the growth of the animals, as the two groups of animals showed the same gains in weight and in length of the tibial bones.

HIGGINS, Boston.

CLINICOANATOMICAL STUDY OF THYMUS. A. STEEGER A., J. ESPINOZA S., and A. DELANO A., Rev. chilena pediat. **24**:1 (Jan.) 1953.

The average weight of the thymus in full-term newborn infants, according to Hammar's index, as well as its microscopic structure, was studied. The authors also investigated the correlation between a large thymus, or status thymicolymphaticus, and the type of evolution of meningococcic infection in 287 children who died of this disease and in 11 cases of sudden death of children during surgical intervention. Finally, they describe five cases of infants in which autopsy revealed absence of the thymus.

FROM THE AUTHORS' SUMMARY.

HAND-SCHÜLLER-CHRISTIAN DISEASE. SANTIAGO MUZZO PONS, Rev. chilena pediat. **24**:118 (April) 1953.

A typical case of Hand-Schüller-Christian disease is reported in a 3½-year-old child. The characteristic triad of "map" skull, exophthalmos, and diabetes insipidus was present. The diagnosis was confirmed by the respective laboratory tests. The author reviews the national literature regarding this entity and also makes a short study of the chronic xanthomatoses, particularly Hand-Schüller-Christian disease.

FROM THE AUTHOR'S SUMMARY.

Diseases of Ductless Glands; Endocrinology

MAINTENANCE MANAGEMENT OF ADDISON'S DISEASE WITH INJECTIONS OF "LONG-ACTING" MICROCRYSTALLINE ESTERS OF DESOXYCORTICOSTERONE. S. Z. SORKIN and L. J. SOFFER, Metabolism **2**:404 (Sept.) 1953.

While the implantation of DCA (desoxycorticosterone acetate) pellets has proved to be an efficient method of controlling the symptoms of Addison's disease over long periods of time, this method of treatment has the following shortcomings: 1. The implantation must be carried out under sterile conditions, necessitating that the patient be admitted to the hospital for each implantation (annually or semiannually); 2. the preparation of pellets is expensive and difficult, and 3, sterilization of the pellets is difficult to carry out and may lead to changes in the pellets which may influence the rate of absorption.

The elaboration of "macrocrystals" or "crystules" of DCA which, on injection, were slowly absorbed led to a series of trials by the authors in 1950. Single injections in adrenalectomized animals and in patients proved to have prolonged and satisfactory effects. In patients, injections of 50 to 100 mg. of DCA crystules suspended in methyl cellulose resulted in maintenance of good health for periods of approximately four weeks. Here again, however, there was a major disadvantage in that the size of the crystals (0.15 to 0.43 mm. in diameter) made the injection difficult.

More recently it has been shown that esters of desoxycorticosterone other than the acetate have more prolonged activity. The present report deals with the results of injections of DCTA (desoxycorticosterone trimethylacetate) and DCPA (desoxycorticosterone phenylacetate). These substances are injected intramuscularly without difficulty through 20 gage needles.

The 97 injections given (25 to 125 mg.) have maintained 10 patients with Addison's disease in good health for periods ranging from 3 to 18 months. Each injection was followed by a period (averaging 5 weeks for the group) of satisfactory response. There were eight exceptions to this rule, which were ascribed by the authors to low dosage, development of respiratory infection, injudicious strenuous work by the patient in hot summer months, and the withholding of the cortisone required for "optimum maintenance treatment."

As a general rule, 60 to 75 mg. of the DCTA or DCPA was required per monthly injection for each mg. of DCA required daily previously. The patients were all given small daily supplements of sodium chloride.

KAPLAN, New York.

TREATMENT OF CONGENITAL ADRENOGENITAL SYNDROMES WITH CONTINUED CORTISONE TREATMENT. A. PRADER, Helvet. pædiat. acta **8**:386 (Nov.) 1953.

Ten girls and 4 boys with congenital adrenocortical hyperplasia, from 3 to 37 years old, were treated exclusively with cortisone for from 3 to 20 months. The mean period of treatment was 13 months (as of June, 1953).

Cortisone was given orally (three times daily), intramuscularly (one injection every one to four days), and in the form of a new long-acting preparation (one injection every month). The treatment was successful and without any complications, with a maintenance dose corresponding to the minimal amount of cortisone that was necessary to keep the urinary 17-ketosteroids just below 8 mg. (Wilkins) in older children and that did not inhibit growth too much in younger children. One injection every month of the long-acting cortisone, which kept the 17-ketosteroids for two weeks between 4 and 7 mg., was also successful. The daily oral maintenance dose in children is about 4 mg. per year of age. The maintenance dose of regular and of long-acting cortisone is smaller.

The clinical results are as follows: disappearance of acne in one to two months; development of breasts in about two months and menstruation after three to seven months in all girls whose bone age is corresponding to normal puberty; feminization of facial expression in all of the females and feminization of body countours in some of them; testicular maturation in older boys and decrease in size of testicular tumors (intratesticular hyperplasia of adrenocortical-like tissue); decrease of hirsutism in older girls and prevention of hirsutism is younger children; improvement of the deep voice in some of the older girls; disappearance of increased pigmentation; inhibition of increased growth and bone development; normalization of the increased hemoglobin values, and improvement of the endocrine psychosyndrome.

After withdrawal of cortisone, the 17-ketosteroids increased again, and the clinical symptoms reappeared. The increase of the 17-ketosteroids is rapid after a short treatment and slow after a long treatment. Nevertheless, the maintenance dose could not be reduced in any case but had to be increased in some younger patients.

The hypothesis of an insufficient production of S hormone, the significance of the often decreased FSH excretion, and the inhibiting effect of cortisone on the production of corticotropin (ACTH) and androgens are discussed. Cortisone treatment is probably not only a hormone-suppression therapy but also a hormone-substitution therapy.

With our present knowledge, congenital adrenocortical hyperplasia and adrenal insufficiency are the only specific endocrine indications for cortisone. The treatment seems to be without danger, but caution is necessary, especially in infants. In order to obtain a somatic and psychic development as normal as possible, treatment should be started early in childhood and continued regularly for years. A constant supervision of the 17-ketosteroids, of growth and bone development of blood pressure, and of body weight is absolutely necessary. The difficult problem of whether older patients should be treated and of whether the probable appearance of fertility is desirable should be decided individually.

FROM THE AUTHOR'S SUMMARY.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

STUDIES ON THE RATES OF INVOLUTION AND RECONSTITUTION OF LYMPHATIC TISSUE. JULES A. FRANK, LINDY F. KUMAGAI, and THOMAS F. DOUGHERTY, Endocrinology **52**:656 (June) 1953.

Marked lymphatic tissue involution has been demonstrated under conditions of inanition, irradiation, and chronic treatment with adrenocortical hormones. Starvation provides certain unique advantages for the investigation of adrenocortically mediated acute lymphatic tissue involution. It is now known that (1) loss of lymphatic tissue weight during a period of inanition begins earlier and proceeds at a more rapid rate than that of other body tissues, and (2) the rate of release of nitrogen from lymphatic tissue in the starved animal is under adrenocortical hormone control.

Although there is an extensive amount of literature on the involution of lymphatic tissue produced by inanition, little is known concerning its reconstitution. A series of experiments was designed to compare the influences of fasting and refeeding on lymphatic tissue of intact and adrenalectomized mice.

The data obtained support the suggestion that lymphatic tissue protein is made available for metabolic use by adrenocortical mediation. It is also suggested that the fasting-refeeding method of study can be used as a method for the bioassay of compounds and/or nutritional factors which produce either involution or growth of lymphatic tissue.

JACOBSEN, Buffalo.

CLINICAL HISTOLOGIC AND ELECTRICAL STUDIES IN MUSCULAR DYSTROPHIES. A. J. ARIEFF and W. R. KIRSCHBAUM, Neurology **3**:35 (Jan.) 1953.

Arieff and Kirschbaum examined seven patients with progressive muscular dystrophy and five patients with myotonic dystrophy clinically and histopathologically.

Familial or hereditary factors were found in two cases of progressive muscular dystrophy and in two cases of myotonic dystrophy. Pseudohypertrophy was seen in four cases of progressive muscular dystrophy and in one unusual case of myotonic dystrophy with myositis. Testicular atrophy, baldness, and cataracts, single or combined, were frequently observed in myotonic dystrophies and were absent in progressive muscular dystrophy. Progressive muscular atrophy may have progressed to degeneration of the spinal motor neurons in two cases. Spinal cord changes in myotonic dystrophies were not observed.

The histologic criteria for a primary myodegeneration include normal nerve fibers and well-preserved motor end-plates in and about degenerating muscle fibers. This degeneration is limited to portions of the bizzare-shaped, swollen, or shrunken fibers, which soon lead to a disorganized reaction of the muscle nuclei and excessive local amitotic multiplication, with formation of nuclear clusters. Transverse and longitudinal clefts of the muscle fibers appear. The perimysial connective tissue was found to be rather inactive, as was the phagocytic reaction of the reticuloendothelial system. There was no histologic difference between idiopathic and myotonic dystrophy.

Electrical studies were done in 13 cases; 7 were diagnosed as cases of progressive dystrophy, including 1 mixed case with spinal atrophy; 6 were myotonic dystrophy. The results are given in detail. From their findings the authors conclude that myotonic dystrophy has characteristic electrical changes, in contrast to progressive muscular dystrophy.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

Diseases of Eye

CONGENITAL STATIONARY NIGHT BLINDNESS WITHOUT OPHTHALMOSCOPIC OR OTHER ABNORMALITIES. F. D. CARROLL and C. HAIG, A. M. A. Arch. Ophth. **50**:35 (July) 1953.

Carroll and Haig describe night blindness present at birth, stationary, occurring in an approximately equal number of males and females, and with no associated abnormalities. Nineteen pedigrees of this disease had previously been reported by Bell. The authors describe a family with this form of congenital stationary night blindness. Dark-adaptation tests, absence of the Purkinje phenomenon, electroretinography, and clinical studies indicated a complete lack of rod function. An unusual opportunity was thus presented for the study of the visual capacity of persons who have normal (or almost normal) cone function only. In peacetime these people are occasionally embarrassed by their handicap, but they marry, have children, and lead almost normal lives; in wartime, however, it is important for the ophthalmologist to recognize the condition so that those affected will not be so placed that their disability may endanger themselves or others.

SPAETH, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

Cutaneous Diseases; Allergy

THE ANEMIA IN LEINER'S DISEASE. K. FRANK, Ann. pædiat. **180**:172 (March) 1953.

The anemia in Leiner's disease (erythrodermia desquamativa) is, according to our findings, not a simple secondary anemia, but a megalocytic one which yields to vitamin B_{12} treatment. This treatment, combined with plasma medication, is sufficient to cure uncomplicated cases completely and speedily, but it is at the same time advisable to keep to a restricted diet.

More striking than the cure of the anemia with vitamin B_{12} is the speedy improvement of the skin and the general health of the patients. This fact emphasizes the importance of vitamin B_{12} in the pathogenesis of the illness and strengthens our assumption that Leiner's disease is primarily a deficiency disease, probably combined with a metabolic upset in the liver-pancreas system.

FROM THE AUTHOR'S SUMMARY.

NUTRITIONAL ALLERGY, ESPECIALLY COWS' MILK ALLERGY, IN INFANTS. M. VEST, Ann. pædiat. **181**:277 (Nov.) 1953.

Nine cases of cows'-milk allergy and one case of allergy to bananas are described.

A leucocytosis was found, with a strong shift to the left, and later eosinophilia was present.

The Prausnitz-Küstner reaction was positive in two cases. There will be a separate report on the findings of antibodies and their importance.

There was an allergy to soya protein in one case, in addition to the cows'-milk allergy.

While, generally, the transition to soya feeding was carried out easily and successfully, it was necessary to feed the last patient on wheat germ, oats, vegetables, fruit, and Ossopan as calcium sources. The child made excellent progress, and the allergy disappeared.

FROM THE AUTHOR'S SUMMARY.

ALLERGIES DUE TO MERCURY. A. PEREZ SOLER, Arch. pediat., Barcelona **3**:737 (May-June) 1953.

The author reviews some of the literature on the effect of mercurial drugs, commenting that the Arabs knew about much of it a thousand years ago. The author confines himself to allergic manifestations and classifies the manifestation of mercury allergies into early and late symptoms. Under early symptoms are the lesions due to external application. Under internal ingestion he includes typical acute mild mercurous chloride (calomel) sickness and atypical illnesses which may be complicated by meningimus, anaphylactic purpura, nephrosis erythroderma, persistent pigmentations, etc. If given by vein it may cause anaphylactic shock.

Late symptoms include lipid nephrosis, agranulocytosis, and neuroallergic diseases, such as polyradiculoneuritis and acrodynia.

He gives two case studies from early infancy and says prevention is better than any treatment, although dimercaprol (BAL) has been very effective in cases of acrodynia.

ALLEN, Santa Fe, N. Mex.

Surgery and Orthopedics

INDICATIONS FOR EMERGENCY SURGERY IN THE NEWBORN AND THE INFANT. JUAN PICANOL, Rev. españ. pediat. **9**:73-94 (Jan.-Feb.) 1954.

In a rather detailed manner, the author discusses the need for urgent surgical intervention in congenital defects which were formerly not amenable to surgery. The second part of the article discusses surgery of an emergency nature for infants. These latter are not congenital in origin.

Among the congenital defects described as to symptoms, radiological findings, and surgical procedure are esophageal atresia, lobar emphysema, hernia through the diaphragm, intestinal atresia, failure of the intestine to rotate, meconium ileus, anorectal malformations, omphalocele, and others.

Among the conditions occurring later are intussusception, appendicitis, certain foreign bodies, strangulated hernia, torsion of spermatic cord, and others less common.

The discourse is well illustrated by x-rays and other cuts taken from cases in the author's own experience.

ALLEN, Santa Fe, N. Mex.

TREATMENT OF BURNS WITH PLACENTAL EXTRACT. LUIS ABERASTURIS CABRERA, Arch. med. inf. **23**:123 (April, May, June) 1954.

The author makes a contribution to the local treatment of burns, and it is his purpose to show how easy this method is. He uses placental extract prepared by Filatov's method. In the comparison with other's therapeutic methods, he elects this method because it's simple, easy, and useful.

FROM THE AUTHOR'S SUMMARY.

Teeth and Dentistry

IS SODIUM FLUORIDE BEST FOR TOPICAL APPLICATION? MAURY MASSLER, J. Dent. Child. **21**:14 (May 25) 1954.

Whether you as a dentist belong to the conservative thinking group that feels that the use of sodium fluoride for a topical application should be used only by the research groups, or whether you advocate its unlimited use, one cannot help but feel that Maury Massler presents stimulating results from his investigation. This article deals with the action of various fluoride compounds in inhibiting the action of acids in the mouth. Sodium silicofluoride was approximately 400 times more effective than sodium fluoride when applied topically to the enamel. The experimental work on the enamel surface of freshly extracted teeth was intelligently done and deserves careful reading by the practicing dentist.

WHITFIELD, Evanston, Ill.

EXPERIMENTAL DENTAL CARIES: V. THE EFFECTS OF DESALIVATION AND CASTRATION ON CARIES AND FLUORINE STORAGE IN THE RAT. DAVID BIXLER, JOSEPH C. MUHLER, and WILLIAM G. SHAFER, J. Nutrition **52**:345 (March 10) 1954.

Bixler and co-workers reported the effects of desalivation and castration on dental caries and the storage of fluorine in the skeletal system of rats. Desalivation resulted in a marked increase in the incidence and severity of dental caries. Castration in both sexes reduced caries development. A sex difference in the storage of fluorine was noted, with females storing higher amounts than males. These experiments serve to emphasize the point that mineral metabolism is greatly influenced not only by the amount of food ingested but also by the growth process as manifested by the assimilation and utilization of food, as well as by the influences that the endocrine system may exert in the metabolism of food and food products.

FREDEEN, Kansas City, Mo.

THE EFFECT OF CARBOHYDRATE-FREE AND CARBOHYDRATE-LOW DIETS ON THE INCIDENCE OF DENTAL CARIES IN WHITE RATS. JAMES H. SHAW, J. Nutrition **53**:151 (May 10) 1954.

James H. Shaw presented data that the two carbohydrate-free diets and the low-carbohydrate ration which he used in these experiments were found to be completely incapable under the conditions in his laboratory of producing carious lesions in a caries-susceptible strain of rats. This was true not only in intact rats, but also in desalivated rats which were maintained on these diets for as long as one and two years.

FREDEEN, Kansas City, Mo.

SOME ASPECTS OF THE USE OF PACIFIER AND DENTAL DECAY. A. SYRRIST and P. SELANDER, Nord. med. **50**:1003 (July 16) 1953.

The authors present a study of 1,332 children, 10 months to 5 years of age, at the Child Welfare Center, Malmö, with regard to their habit of using a dummy pacifier, and a correlation of these findings with the condition of their teeth. In addition, special examinations were carried out on 103 children of the same age who were selected because of their exceptionally poor dental condition. The investigation yielded the following results: Pacifiers were used by 34% of the children; 18% used a pacifier only before 10 months of age; 6% used a sugar pacifier, 3% even after 10 months of age. In the poorest social class, the pacifiers were more common than in the other social classes. Children who employed an ordinary pacifier had, at 3 to 5 years of age, a poorer dental condition than those who had not used a pacifier. The difference is significant. This difference may be due to the fact that in the social class from which most of the pacifier children come, deleterious factors for tooth decay are most frequently encountered. Children who used sugar pacifiers showed a significantly greater risk of developing a poor dental condition than those without pacifiers. Thus 15% of 648 children between the ages of 3 and 5 years exhibited a poor dental condition, while the corresponding rate in 36 children with sugar pacifiers, even when used after 10 months of age, was a little over 50%. Children with exceptionally poor deciduous occlusion had employed sugar pacifiers significantly more often than children with good dental occlusion.

WALLGREN, Stockholm.

Miscellaneous

RECTAL ADMINISTRATION OF SODIUM THIOPENTONE TO CHILDREN. IAN H. MCDONALD, M. J. Australia **1**:174 (Feb. 7) 1953.

Thiopental sodium has been used extensively as a basal anesthetic in children of two to seven or eight years at the Melbourne Children's Hospital. Below the 2-year level it is felt to be psychologically unnecessary.

Results showed that the drug had considerable value and was much easier to use than tribromoethanol (Avertin). Complications from its use are few. Psychologically, fear of further anesthesia was three times as great in the control series as in the group in which thiopental sodium was used.

MCGUIGAN, Evanston, Ill.

THE TWO TYPES OF WALKINGS: AUTOMATIC WALKING OF THE NEWBORN WITH SUBCORTICAL REGULATION, DEFINITIVE AND FREE AUTONOMIC WALKING UNDER CORTICAL CONTROL AND DEFINITIVE WALKING OF THE DAILY TRAINED INFANT. ANDRÉ-THOMAS and MLLE. AUTGAERDEN, Presse méd. **61**:582 (April 22) 1953.

After a full and illustrative description of the automatic walking of the newborn and the definitive walking of the daily trained infant, the author points out that the duration of the automatic walking is variable and may be prolonged as a consequence of changes in the cortex. The infant backward in psychomotor development may show for a long time the primary type of walking shown by the newborn.

Observations were made of the persistence of this primary type of walking for several months and of its disappearance with no replacement by definitive walking in cases in which the psychomotor progress was almost null. This was generally due to extensive and diffuse lesions of the cortex, but there are cases in which the process is more localized and induces hemiplegia; yet, the infant succeeds in walking by combining the abnormal movements of the paralized and contractured lower limb with the normal movements of the healthy limb, although the innate aptitudes have been compromised. Admittedly, the spared portions of the cerebral cortex can make up remarkably for an imposed deficiency by organizing substitutions; this leads to the conclusion that backwardness does not mean inability.

FROM THE AUTHORS' SUMMARY.

Books

Pediatric Problems in Clinical Practice. Edited by H. Michal-Smith. Price, $5.50. Pp. 310. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1954.

In recent years there has been a generally accepted trend toward a philosophy, in the teaching of pediatrics as well as in the clinical approach, of regarding the child as a complete entity. This is in distinction to earlier views, which considered him as to various divisions of his anatomy or in the light of the pathologcal effects of infectious diseases upon him. There remains little opposition to this modern view, and entirely broader horizons have been uncovered which have been to the advantage of the child patient, as well as of the viewer.

This book is written with this theme as its main concept. The child is considered in the background of his disability, whether it be physical, mental, or emotional. Fourteen of the common categories of handicapped states are discussed in as many chapters, each written by special authorities in their respective fields. The Normal Child is first described, followed by discussions of the Sick Child, the Emotionally Disturbed Child, the Schizophrenic Child, the Mentally Retarded Child, the Brain-Injured Child, the Cerebral Palsy Child, the Orthopedically Handicapped Child, the Allergic Child, the Cardiac Child, the Diabetic Child, the Epileptic Child, and the Tuberculous Child.

It is to the problems of these children that this book is addressed. As Dr. Howard A. Rusk states in the Foreward, "There has been a growing interest in the development of services which will permit the child with a mental, physical or emotional disability to live within the limits of his disability, but to the hilt of his capacities." As the authors of this book point out, we can now approach with confidence many disabling conditions which even a few years ago were generally accepted as hopeless.

The authors vary, as would be expected, in their specific writing skills and in their approach to the technical discussions. However, one would not need be a candidate for the American Board of Neurology and Psychiatry to be able to follow the discussions presented, especially if one is equipped with a good training in pediatrics. Not only the medical aspects of the aforementioned entities receive thorough attention, but also the psychological factors are correlated which permeate the care and rehabilitation of the handicapped. This combined knowledge of both approaches is brought to pediatricians, to all physicians, psychologists, social workers, and teachers—all those interested in the health and concerned with the welfare of children.

Until the present time, most physicians have had to rely upon their own ingenuity for directions to the family of a handicapped child. Curiously enough, in this fragmentary information obtained from the background of his experience and his acquired sympathy for the handicapped, the physician has found much of this advice to be sound and surprisingly humane, but always inadequate. Between the covers of this book he can now find amplification of his views and perhaps an explanation for some of the dubious features of some of his problems. In this material, the neophyte might browse and become oriented for that which lies in store for him in the future, thereby saving himself some mistakes of judgment which otherwise would be his lot. This book belongs in the reference library of every practicing pediatrician and physician, and it should be made available to all social workers and physical therapists, as well as others who have to do with the handicapped child.

One of the most valuable sections of this book is the recently compiled bibliography for the parents of these children. It comes as a bountiful blessing to physicians who have always sought to guide the reading of intelligent parents of these unusual children, who search constantly for an orientation by reading to help solve their special problem and thus to understand it the better.

Prematurity, Congenital Malformation and Birth Injury: Proceedings of conference sponsored by Association for Aid of Crippled Children at New York Academy of Medicine, 2 E. 103rd St., New York 29, June 5 and 6, 1952. Price, $4. Pp. 225. Association for Aid of Crippled Children, 345 E. 46th St., New York 17, 1953.

In recent years it has become popular for various privately endowed foundations, certain proprietary food and medicine manufacturers, and progressive-minded industrial interests to underwrite and promote symposia and conferences, and invite for participation well-known authorities in the respective fields of interest of the sponsoring agencies. It is a satisfactory and

illuminating technique to get the experts on one subject to sit down together and amiably extoll their own views in the field in which they are interested, together with contemporary workers in the same or related fields. The interested reader and student thus has access to the mass of information presented by such conferences and placed between the covers of one book, instead of being required to search through the literature for the opinions of the same authorities. Here it may be found in compact form, which is of tremendous advantage to the teacher or student who is searching for a résumé or details on a specific subject by a respective authority. One is also impressed with the elasticity of argument and refutation which prevails when these experts are in the presence of their colleagues.

The book under discussion is such a report. It is an edited record of the proceedings of a conference on "Prematurity, Congenital Malformation and Birth Injury," sponsored by the Association for the Aid of Crippled Children and held in New York on June 5 and 6, 1952. Forty-eight distinguished authorities in these fields participated, and the discussion is well organized and presented along the above-mentioned headings.

All of the latest data are discussed on the premature infant, including the nebulous field of the pulmonary hyaline membrane and the disputed interpretation of the so-called "eosinophilic herring," which reputedly drags itself over the path of those who believe in the existence of this entity. The immunological considerations of the premature infant, the hematological aspects of this neonate, the little-known importance of the endocrine glands in the premature baby, and the various factors which have to do with the prevention of premature births—are all well presented. The death rate of the premature baby, largely determined by its early advent into the world, is today the number one public health problem. The death rate of an infant less than one day old is more than 6,000 times that of the 10-year old school child. From the standpoint of national economy, the problems are far more important than those of heart disease and cancer, both of which have been more widely publicized.

The subject of congenital malformation is fully discussed, including experimentally induced anomalies, classification of malformation during fetal life, and a statistical approach to the study of such malformations. It is presumed by the participants of this phase of the symposium that within 10 or 20 years the problem will be taken out of the laboratory and placed in the field of clinical medicine. It is hoped by this group of discussants that in the next 20 years the list of understandable diseases and abnormal conditions which are not infectious will be more clarified and controlled.

The third category of discussion embraces the subject of birth injury. This consists largely of the importance of the pathology of late pregnancy, the various impacts to the fetus and infant of anoxia, and a digestion of the vast amount of data which has accumulated in animal experimentation with anoxia.

It is observed that of the 48 participants experting at this conference, 44 of them come from the area of the United States east of the Allegheny Mountains. Since the interests of the Association for the Aid of Crippled Children are not provincial in scope, the uninformed reader on this point wonders if all of the available expert opinion on these subjects is concentrated east of the 75th meridian in this country.

pediatric forms of choice

of 2 antibiotics of choice

newest

therapy

with these flavor-favorite

forms of

Tetracyn®

Brand of TETRACYCLINE

Oral Suspension *(chocolate flavored)*

1.5 Gm., in 2 oz. (60 cc.) bottles,
supplies 125 mg. / 5 cc. teaspoonful

Pediatric Drops *(banana flavored)*

1.0 Gm. in 10 cc. bottles with special
dropper calibrated at 25 and 50 mg.

established

therapy *with these*

dosage forms of choice

Terramycin®

Brand of oxytetracycline

Oral Suspension *(raspberry flavored)*

1.5 Gm., in 1 oz. (30 cc.) bottles,
supplies 250 mg. / 5 cc. teaspoonful

Pediatric Drops *(raspberry flavored)*

1.0 Gm. in 10 cc. bottles with special
dropper calibrated at 25 and 50 mg.

both antibiotics discovered by Pfizer PFIZER LABORATORIES, Brooklyn 6, N. Y.

DIVISION, CHAS. PFIZER & CO., INC.

For CONSTIPATED BABIES

Borcherdt

MALT SOUP *Extract**

A gentle laxative modifier of milk. One or two tablespoonfuls in the day's formula—or in water for breast fed babies—produce a marked change in the stool.

SAVES DOCTOR'S TIME, TOO!
Fewer phone calls from anxious mothers. Malt Soup Extract is merely added to the formula. Prompt results. Easy for mother to prepare and administer. Does not upset the baby.

*Specially processed non-diastatic malt extract neutralized with potassium carbonate. In 8 oz. and 16 oz. bottles.

Send for Samples and Literature

BORCHERDT MALT EXTRACT CO.
217 N. Wolcott Ave. • Chicago 12, Ill.

PRESCRIPTION SERVICE FOR ALLERGIC DISEASES

Allergenic Extracts, Diagnostic and Therapeutic

Devoted exclusively to the manufacture of pollen, fungus, epidermal, food, dust, and miscellaneous allergenic extracts for the diagnosis and treatment of allergic conditions.

A pollen check list for your state and other literature sent on request.

U. S. Government License No. 103
since 1929

ALLERGY LABORATORIES, INC.
Pasteur Medical Building 1111 N. Lee Ave.
Oklahoma City 1, Oklahoma

Helpful suggestions

SLEEP SHOULD MEAN REST
HOW MUCH DO YOU NEED?
HOW TO PREPARE FOR SLEEP
TEN COMMANDMENTS FOR GOOD SLEEPING

for rest and relaxation

MASTER KEY TO RESTFUL SLUMBER
by J. E. Gibson
8 pages, 15 cents

SO YOU CAN'T SLEEP?
by P. H. Fluck
8 pages, 15 cents

AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET
CHICAGO 10, ILLINOIS

"Extremely well tolerated"

● A physician writes about St. Joseph Aspirin For Children that it is "extremely well tolerated."

As palatability and purity are essential factors in the toleration of any medication, it is easy to understand why these specialized aspirin tablets—combining exceptional palatability with aspirin of the highest quality—are so easy to administer and so extremely well tolerated by children of all ages.

Physicians are finding St. Joseph Aspirin For Children:

1. *Easy to give*
2. *Pleasant to take*
3. *Therapeutically Effective*

ST. JOSEPH ASPIRIN FOR CHILDREN

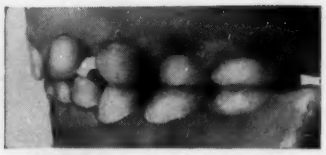
A Palatable Aspirin Tablet of Unique Excellence

A PRODUCT OF Plough, Inc.

If you have not received samples, write to Plough, Inc., Memphis, Tennessee

THUMBSUCKING

since infancy caused this 4 year old's malocclusion.



THUM

TRADE MARK

THUM broke the habit and teeth returned to normal position in 9 months.

Get Thum at your druggist or surgical dealer. Prescribed by physicians for over 20 years.

ACCEPTED FOR ADVERTISING IN PUBLICATIONS OF THE AMERICAN MEDICAL ASSOCIATION

"Doctor, can you tell me . . . ."

What is it? What causes it? How serious is it?

For explanations to these questions and many more, have your patients read:

DIPHTHERIA
by Paul S. Rhoads, 8 pages, 15 cents

SCARLET FEVER
by E. B. Perry, 8 pages, 15 cents

WHOOPING COUGH
by Constance Frick, 4 pages, 10 cents

MEASLES
by A. L. Hoyne, 8 pages, 15 cents

PNEUMONIA
by W. W. Bolton, 12 pages, 15 cents

AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

in hay fever... *in other allergies...*

an
unsurpassed
pediatric
antihistamine

Pyribenzamine® Elixir

A palatable, spice-flavored antihistamine, Pyribenzamine Elixir offers highly effective therapy in a broad range of allergies. *Dosage can be readily adjusted* to any age, any individual requirement. *Prescribe this well-accepted medication* alone or as a therapeutic vehicle. Each 4-ml. teaspoonful contains 30 mg. Pyribenzamine citrate.

Pyribenzamine® citrate (tripelennamine citrate CIBA)

C I B A
SUMMIT, N. J.

7/2097M

SEX EDUCATION

For those
who are
on the
threshold of engagement
or marriage

THE AGE OF ROMANCE

by Thurman B. Rice, M.D.
Training for a happy home life . . paths to unpopularity . . planning for parenthood . . the ideal honeymoon . . making a happy home.
43 pages, 25 cents

GETTING READY FOR MARRIED LIFE

by Howard Dittrick, M.D.
For the engaged person who has begun to seriously consider the responsibilities of marriage . . from personal problems to venereal diseases.
28 pages, 20 cents

MORE HELP FOR CHILDLESS COUPLES

by Joseph D. Wassersug
Two case histories to help convey information on "new techniques," organic and psychologic blocks to conception, and sterility.
8 pages, 15 cents

. . . . . for adults concerned with the instruction of the young people

THE WORD YOU CAN'T SAY

by Hannah Lees
Emotional and physical causes of masturbation in relation to family, friends, normalcy and worry.
8 pages, 15 cents

THOSE FIRST SEX QUESTIONS

by Thurman B. Rice, M.D.
How to acquaint the curious pre-adolescent with the subject of reproduction in a truthful and wholesome manner.
43 pages, 25 cents

THE STORY OF LIFE

by Thurman B. Rice, M.D.
For boys and girls 10 years of age, telling them how the young come to plants, cold-blooded animals, domestic animals and human parents.
36 pages, 25 cents

HOW LIFE GOES ON AND ON

by Thurman B. Rice, M.D.
To help teenage girls prepare for their careers of motherhood . . . progressing through dates, engagement and marriage.
44 pages, 25 cents

THESE PAMPHLETS OFFER HELP IN THE CHALLENGE OF ADJUSTING TO THE SEXUAL SIDE OF LIFE

BUREAU OF HEALTH EDUCATION
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN • CHICAGO 10

Enclosed find $..... for the pamphlet(s) checked at the side.

NAME_____

ADDRESS_____

CITY_____ ZONE_____ STATE_____

- ☐ THE AGE OF ROMANCE, 25 CENTS
- ☐ GETTING READY FOR MARRIED LIFE, 20 CENTS
- ☐ THE WORD YOU CAN'T SAY, 15 CENTS
- ☐ MORE HELP FOR CHILDLESS COUPLES, 15 CENTS
- ☐ THE STORY OF LIFE, 25 CENTS
- ☐ THOSE FIRST SEX QUESTIONS, 25 CENTS
- ☐ HOW LIFE GOES ON AND ON, 25 CENTS
- ☐ A.M.A. PUBLICATIONS ABOUT YOUR HEALTH, FREE

A COMPLETE CATALOGUE OF PUBLICATIONS ABOUT YOUR HEALTH WILL BE SENT TO YOU UPON REQUEST

a really new concept in Infant Feeding

- ✓ A milk formula base designed for pediatric use . . . **and for one specific purpose**—infant feeding.
- ✓ Made from Grade A milk* "the first in infant feeding."
- ✓ Butter fat has been completely replaced with readily tolerated and easily digested fats.
- ✓ Fortified by synthetic vitamins—and added iron.
- ✓ Permits complete flexibility in carbohydrate adjustment.
- ✓ Varamel is ethically promoted and sold only in drugstores.

Milk Products Exclusively for Infant Feeding

THE BAKER LABORATORIES, INC., Cleveland 3, Ohio

Plant: East Troy, Wisconsin

ACCEPTED COUNCIL ON FOODS AND NUTRITION AMERICAN MEDICAL ASSOCIATION

*Made from Grade A milk (U. S. Public Health Service Milk Code) which has been modified by replacement of the milk fat with vegetable and animal fats and by the addition of vitamins and iron. No carbohydrate has been added.

VARAMEL

because safety and nutritional effectiveness count so very much

specify **DEXTRI-MALTOSE**

MANUFACTURED SPECIFICALLY FOR INFANT FORMULAS

Dextri-Maltose is specifically designed for infant formulas—*and only infant formulas.* Unlike many milk modifiers, Dextri-Maltose is palatable but not sweet. It does not cloy the appetite. Infants fed Dextri-Maltose formulas do not develop a "sweet tooth" which may cause later resistance to essential foods.

The dextrins and maltose in Dextri-Maltose, plus the lactose of milk, give the infant a mixture of *three* different carbohydrates. These are broken down at different rates in the intestinal tract. Absorption is gradual. Sudden fluctuations in blood sugar levels are prevented.

Dextri-Maltose® is always kept safe and dependable through meticulous quality control. No other carbohydrate used in infant feeding has such a background of acceptance and dependability.

the importance of adequate added carbohydrate

Added carbohydrate provides calories needed to spare protein for tissue building, to permit proper fat metabolism and promote good water balance. Authorities on infant feeding recommend the addition of about 5% carbohydrate to milk and water mixtures. This proportion of carbohydrate is obtained by adding 1 tablespoon of Dextri-Maltose to each 5 or 6 ounces of fluid.

MEAD JOHNSON & COMPANY
EVANSVILLE, INDIANA, U.S.A.

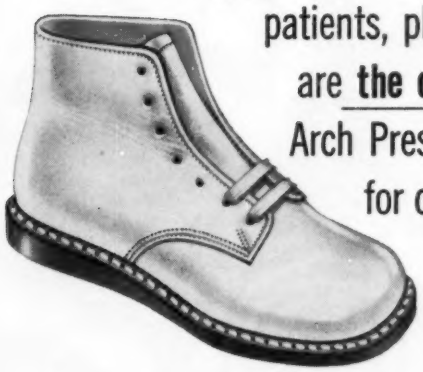
MEAD

Selby*

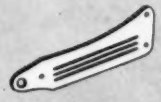
JUNIOR ARCH PRESERVER

Shoes

* when you recommend shoes for your patients, please remember . . . Selby Juniors are **the only genuine** Arch Preserver Shoes for children



Broad Based Heel



Alloy Spring Steel Shank

Wedge Construction

*Selby

JUNIOR ARCH PRESERVER SHOES

● *If Selby Junior Arch Preservers are not available in your city, please write directly to us.*

The Selby Shoe Company

Portsmouth, Ohio

MORE THAN THREE QUARTERS OF A CENTURY OF FINE SHOEMAKING

For Nasal Congestion
in THE COMMON COLD
Physiologically acceptable Neo-Synephrine hydrochloride solution promptly constricts the engorged nasal capillaries which are responsible for nasal congestion in the common cold. When the nasal mucosa is reduced to its normal state, the nasal passages resume their proper patency, drainage is possible, and the patient can again breathe freely.
By its shrinking action on the nasal mucosa, Neo-Synephrine helps to keep the sinuses aerated and the openings to the eustachian tubes clear.
Neo-Synephrine within minutes produces decongestion that lasts for hours.
NEO-SYNEPHRINE®
Hydrochloride
0.25%, 0.5% and 1% Solution
New: Nasal Spray — Plastic Squeeze Bottle